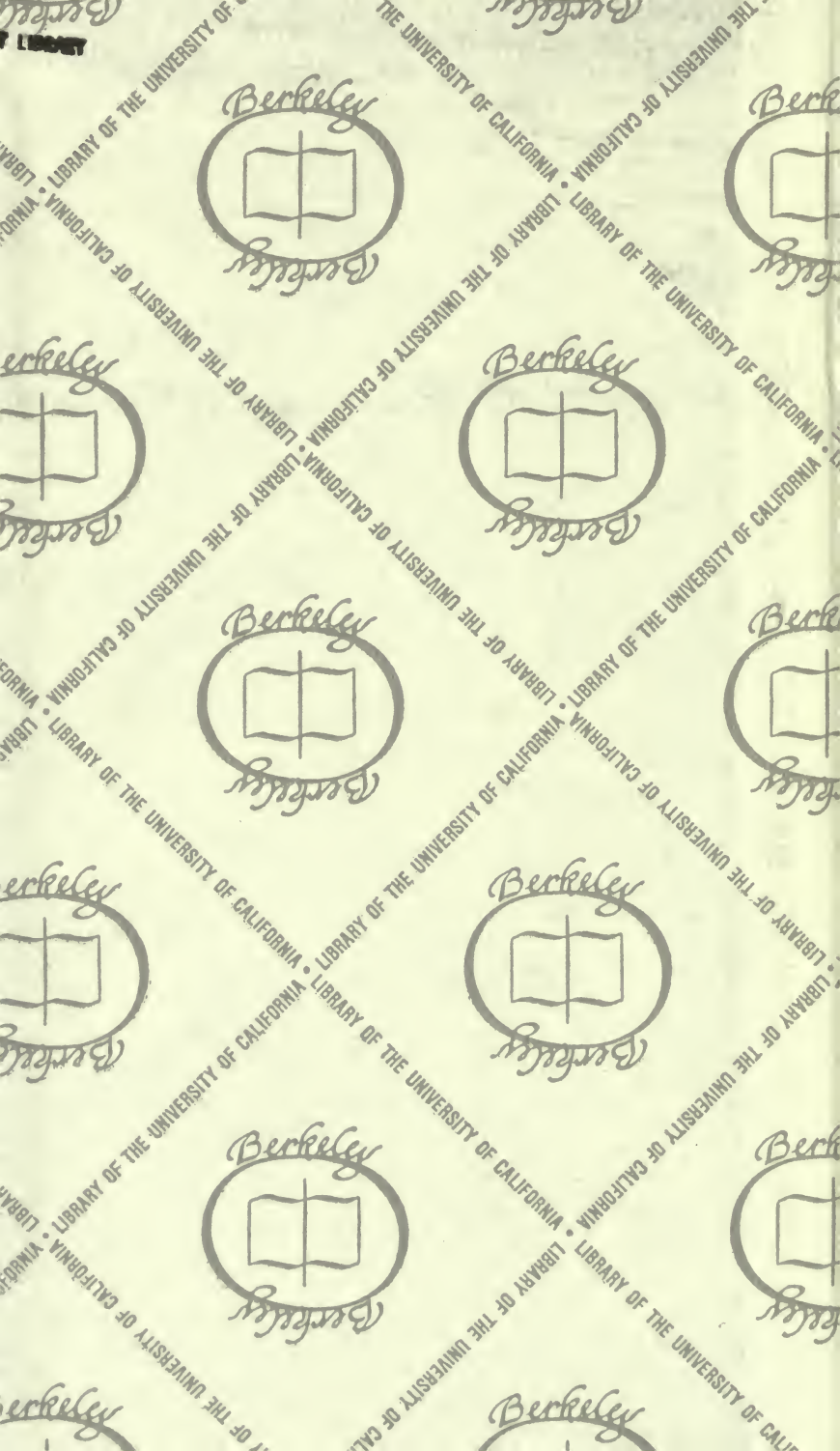
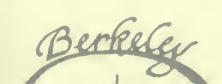
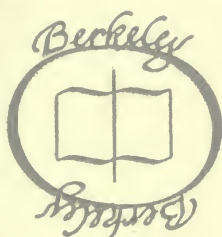
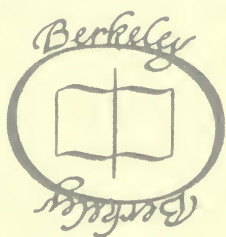
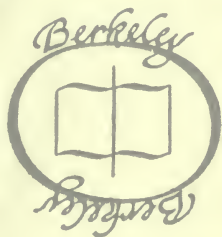






TEXT BOOKS OF PATHOLOGY

EDITED BY

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THE PATHOLOGY OF GROWTH
TUMOURS

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VOL. I. TUMOURS. BY CHARLES POWELL WHITE

THE PATHOLOGY OF GROWTH TUMOURS

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PREFACE

IN the following pages I have endeavoured to deal with the pathology of tumours and the allied subjects of hypertrophy, regeneration, etc.

Throughout the volume I have laid most stress on the physiological aspects of the subject. I have endeavoured to consider, not only the question what? but also the questions how? and why? Considerable space has, therefore, been devoted to such questions as the relation between functional activity and growth, and the origin, life history, and causation of tumours. Similarly the illustrations have been selected to show, not merely the structure of the various tumours, but also the mode of growth and the relation of the tumour to the organism

The illustrations are all original and, except where otherwise stated, are from photomicrographs. Most of them are from my own specimens; others, for the use of which I have to thank Professor J. Lorrain Smith and Dr. W. Mair, are from specimens in the pathological department of the University of Manchester. I am indebted to Mr. J. W. Dunkerley, L.D.S., of Manchester, for the loan of the section from which Fig. 16 was taken. Lastly, I have to express my thanks to Mr. W. Manby, laboratory steward in the pathological department of the University, who has spent much time and trouble in preparing the illustrations for me.

CHARLES POWELL WHITE.

MANCHESTER, 1912.

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CHAPTER I

VARIATIONS IN DEVELOPMENT, GROWTH, AND FUNCTIONAL ACTIVITY

THE several orders of physiological units—organism, organs, tissues, cells—display three primary properties, namely, development, growth, and performance of function.

By development we understand the formation of a structure from a pre-existing structure with different characters. Thus the formation of digestive glands by outgrowths from the primitive alimentary canal implies development. The alteration in the characters of the cells and tissues in the course of development is called differentiation. By growth is meant an increase in the size of a structure without a qualitative alteration in its characters. Both development and growth are characterised by cell proliferation. During development one cell may give rise to other cells with different characters. After development is complete each cell, under normal conditions, gives rise only to cells of like characters to itself.

Development and growth may co-exist and, in the majority of animals, both normally come to an end after a certain period of time, but growth may continue in a structure the development of which is complete. In certain animals—e.g. in some fish—it appears that growth may continue throughout life without a definite limit, but, with this exception, each species of animal has its own

limits of development and growth as regards organism, organs, tissues, and cells, which limits have been determined during the progress of evolution. Thus each species of animal has a certain general complexity of development and a certain size, but individuals of the species may, within limits, show variations in either direction from the mean.

Although the organism is composed of cells, it is not to be regarded merely as a cell aggregate. It is more correct to regard the cell as a part of the whole organism. The life of the organism is not the summation of the life of the component cells, but rather the life of the cell is part of the life of the organism. During development and growth the cells behave, not as individual units, but as component parts of the whole. The organism does not grow because the cells multiply, but the cells multiply because the organism grows. During development and growth the various tissues remain confined to their proper situations and the amount of each is similarly limited. In other words, the development and growth of the cells, tissues, and organs are co-ordinated as regards the amount and position of each constituent, so that growth and development must be regarded as properties of the organism as a whole.

How this co-ordination is effected we do not know. It has been shown that the majority of the cells in the body are joined together by delicate intercellular bridges or processes—e.g. the prickles of prickly cells—and it seems probable that through these communications influences may pass from cell to cell and that the co-ordination may be effected in this way. It is known that in plants such influences pass from cell to cell by strands of protoplasm which, passing through apertures in the cell walls, unite the protoplasm of adjacent cells. It is, perhaps, natural to suggest that the co-ordination might be effected through the nervous system, but that the nervous system is not necessary is shown by the fact

that the co-ordination exists in the early stages of development before the nervous system itself is formed. The nervous system is concerned with the co-ordination of function rather than with the co-ordination of structure. By function we mean the work which the different parts of the body perform. The function of any part is directed towards maintaining the life of the organism or of the species and the functions of the different parts are co-ordinated by the nervous system and by the circulation and, in some cases, by the intercellular connections.

An important property of living things is that known as physiological or functional *inertia*. This closely corresponds with the physical inertia met with in mechanical science. A cell or organ which is in a state of rest or activity does not at once respond to a stimulus which tends to alter that state, but a period known as the latent period intervenes between the stimulus and the response. Similarly the state induced by the stimulation continues for a time after the cessation of the stimulus. Thus stimulation of the vagus leads to inhibition of the heart-beat which comes on after a certain latent period. When the stimulation ceases the heart continues in the state of inhibition for some time before the beats are renewed. These phenomena of inertia are of great importance in enabling us to understand physiological and pathological processes. It is by means of inertia that the organism is able to adapt itself to changing conditions as seen, for example, in the production of compensatory hypertrophy and immunity.

The three properties, development, growth, and functional activity may show variations in either direction from the normal, and we have now to consider the conditions under which these variations occur. Here, as in other branches of the subject, we find that there is no sharp division between physiology and pathology. Some of the processes to be discussed are purely physiological,

while others are pathological. The variations to be considered are as follows :

1. *Variations in functional activity*.—Functional activity may be absent (*anergasis*), diminished (*hypoergasis*), increased (*hyperergasis*) or changed in character (*metergasis*). Thus a muscle may contract more, or less, forcibly than normal ; a gland may produce more, or less, secretion, or may produce a secretion of a character different from the normal.

2. *Variations in the size of an organ without alteration of its structure*.—These may be due to variations in development or to variations in growth. There may be complete absence of development (*aplasia*), or development may be incomplete (*hypoplasia*) or excessive (*hyperplasia*). On the other hand, if the organ diminish in size we have the condition *atrophy*, while if it grow larger than normal it is said to undergo *hypertrophy*. Leaving on one side, for the present, the conditions aplasia, hypoplasia and atrophy, the conditions of hyperplasia and hypertrophy are distinguished as follows.

In hyperplasia of an organ we have a development of new constituent parts of the organ (lobules, etc.), while in hypertrophy we have an overgrowth of the constituent parts already present. Hypertrophy is sometimes divided into simple hypertrophy or overgrowth by enlargement of the individual cells, and numerical hypertrophy or overgrowth by proliferation of the cells, and numerical hypertrophy is usually called hyperplasia as well as the true hyperplasia above mentioned. The two forms of hypertrophy are, however, essentially the same, and usually occur together, while they are distinct from true hyperplasia. This will be made clear by taking the kidney as an example. A kidney which is the seat of hyperplasia is enlarged, but otherwise normal, in appearance. The enlargement is due to the formation of an increased number of tubes and glomeruli, each tube being, in itself, normal. Such a

kidney will appear perfectly normal under the microscope, the proportion of glomeruli to the convoluted tubes being the same as in a normal kidney. On the other hand, in a kidney which is hypertrophied there is no formation of new tubes and glomeruli, but only an enlargement and elongation of pre-existing structures accompanied by proliferation of the epithelial cells. Hence such a kidney will present fewer glomeruli in proportion to the space occupied by the convoluted tubes, the glomeruli being separated by the elongation and consequent increased convolution of the tubes, the tubes and glomeruli being otherwise normal in appearance.

In atrophy the organ is smaller than normal owing to a diminution in size of the constituent parts. Thus an atrophied kidney would show a crowding together of glomeruli owing to the diminution in size of the convoluted tubes. In all these conditions the general structure is unaltered except as regards size, but other conditions (degenerations, etc.) may be associated with them.

3. *Variations in the proportion of one tissue to another in a single organ.*—These usually consist in an increase of the supporting tissue at the expense of the specialised tissue (*fibrosis, gliosis*). Sometimes the blood or lymph vessels are dilated (*angeiectasis*).

4. *Alterations in the characters of the tissues (metaplasia).*—For example, cartilage or bone may appear in fibrous tissue, columnar epithelium may become changed into squamous, and endothelium may take on the characters of different types of epithelium.

When we come to consider the conditions under which these different variations are met with, we find that they may be placed in two classes—adaptive and progressive variations. Adaptive variations are those which occur in adaptation to alterations in the sur-

rounding conditions and are necessary to the well-being of the individual or species. These changes are strictly physiological in character, although often occurring as the result of pathological conditions. Progressive changes, on the other hand, are in excess of the needs of the organism, and are harmful and pathological in character.

Adaptive Variations.

It is one of the primary characters of all living things that they are able to adapt themselves to alterations in the surrounding conditions. Without this power of adaptation life would be impossible. The adaptation may show itself during the life of the individual or during the existence of the species. Adaptation occurring during the existence of the species may be attributed to natural selection and heredity. We do not, however, know the exact process by which adaptive changes are effected in the individual, at least in the majority of cases. All adaptive changes are more complete in the young than in the adult.

Adaptive changes in functional activity.—The functional activities of different parts of the body are co-ordinated for the most part by the nervous system. In some cases co-ordination is effected by means of substances (hormones) circulating in the blood. All organs are so constructed that, under normal conditions, their functional activity is not exerted to the utmost. In other words, there is always present a reserve force which can be brought into action upon an emergency. A man of poor muscular development may, in an attack of mania, show such strength that it requires the efforts of several strong men to restrain him. Again, if one kidney is removed the other immediately shows a great increase of functional activity. Supporting structures, also, are capable of bearing a much greater strain than is usually thrown upon them.

The continuance of a normal condition of functional activity depends on a continual exercise of this function, otherwise the functional activity diminishes. A moderate repeated exercise of the function to an extent above what is necessary for the normal condition leads to an increased power of functional activity and to an increased limit to the reserve force. On the other hand, excessive functional activity leads to exhaustion. Under certain conditions adaptation is also possible in respect to an alteration in the character of the function. Thus the secretion of the digestive glands adapts itself, within certain limits, to the nature of the food to be digested, and, when the function of the kidneys is seriously impaired, the sweat glands may excrete urea.

Adaptive variations in the size of organs.—Adaptive hypertrophy and hyperplasia occur under two conditions : (A) as a result of increased functional activity ; (B) in anticipation of increased functional activity.

(A) Adaptive hypertrophy as a result of increased functional activity is called *work*, or *compensatory*, *hypertrophy*. We have seen that an organ is capable of exerting its function to an extent in excess of the normal amount. If this increased functional activity is repeatedly exerted to a moderate amount the organ undergoes hypertrophy, and, in doing so, becomes capable of a still further increase in its functional activity. This increase has a limit beyond which it is impossible to go, but the limit differs widely in different people. Some men leading sedentary lives and taking little exercise may have large and well-developed muscles, while others who habitually have much muscular work to perform may have small muscles. The normal standard of development and growth for each individual depends partly on his inborn characters and partly on the extent to which his organs are used. Hypertrophy following on hyperergasia continues only as long as the increased functional activity continues.

If the functional activity of any part is diminished

instead of being increased, the result is that the organ undergoes atrophy. This form of atrophy is known as *disuse atrophy*. If, for example, a limb be amputated, the muscles, nerves, blood vessels, etc., passing to the limb become atrophied from disuse and the corresponding nerve centres in the spinal cord also atrophy.

If the functional activity is excessive we find that the organ atrophies from overwork. This is seen in the occupation paralyses, such as writer's cramp, etc.

Muscles.—The extent to which the skeletal muscles may hypertrophy as a result of increased work is well known. Familiar examples are the blacksmith's arm, the cyclist's thigh, the general muscular development of athletes. The hyperergasia in a muscle which leads to hypertrophy may be the result of a voluntary impulse or it may be the result of a loss of function in other muscles. The hypertrophy is due to an enlargement of individual fibres rather than to an increase in their number.

Skeletal muscles also show disuse atrophy as, for example, the general atrophy in bedridden patients and the atrophy of the muscles in a limb in which the joints are ankylosed.

The visceral muscles, especially the hollow muscular organs, also show work hypertrophy. The increased work is usually the result of some obstruction to the lumen, either of the organ itself or of some tube leading from it. The obstruction prevents the free flow of the contents of the organ so that more work is thrown upon the muscle in carrying out its function. In these cases the hypertrophy may be very great, the muscular wall becoming many times the normal in thickness. Thus the bladder hypertrophies when there is obstruction of the urethra from enlarged prostate, stricture, or calculus, and in intestinal obstruction the intestine hypertrophies above the obstruction. The heart especially shows hypertrophy when the amount of work performed by it is

increased owing to (a) increase in the blood volume, (b) a demand for a more vigorous circulation as in athletes, (c) increased blood pressure as in Bright's disease, (d) obstruction to the circulation as in disease of the aorta or arteries and in pulmonary emphysema, (e) disease of the valves so that the proper working of the organ is affected, (f) pericardial adhesions leading to increased work thrown on the muscle during contraction, owing to the fact that the muscle fibres have to contract against the resistance offered by the adhesions within and without the pericardial cavity.

Glands.—Secreting glands undergo compensatory hypertrophy when their functional activity is increased. Thus, the kidneys hypertrophy in those who habitually drink large quantities of fluid and in diseases accompanied by a large excretion of urine such as diabetes. When one kidney is removed or destroyed more work is thrown on the remaining kidney, so that it hypertrophies until it is eventually able to perform the work normally carried out by both organs. The amount of hypertrophy is often considerable, but it seldom or never attains fully the size of both organs combined. Similarly in atelectasis of one lung the other hypertrophies. The liver also shows a great capacity for undergoing hypertrophy. As much as three-quarters of the liver may be removed and yet the remaining quarter may hypertrophy so that the original size of the organ is restored.

Occasionally when one gland is removed or destroyed another gland of a different nature may take on the function of the lost gland and may hypertrophy in consequence. For example, hypertrophy of the pituitary has been found after removal of the thyroid. This form of hypertrophy is known as *vicarious hypertrophy*.

Blood-forming organs.—Akin to the glandular organs are the blood-forming organs—spleen, lymph glands and bone marrow. These all show compensatory hypertrophy consequent on increase of functional activity.

They also show vicarious hypertrophy as is seen in the hypertrophy of the lymph glands and marrow after removal of the spleen.

Protective and supporting structures.—When the skin is exposed to increased pressure or friction both the epidermis and the dermis become hypertrophied. Similarly tendons and bones become hypertrophied when increased strain is thrown upon them. If the increased pressure or strain is too great or is continuous the result is atrophy as is seen in bedsores. When one leg has been removed the other becomes markedly hypertrophied owing to the increased strain. Similarly these protective and supporting structures show disuse atrophy.

Nervous system.—The occurrence of work hypertrophy in the nervous system appears open to doubt, but it is stated that the brains of brain-workers are larger than those of manual workers. Disuse atrophy, however, occurs in the central nervous system and in the peripheral nerves as the result of amputation of a limb, etc.

The mechanism of work hypertrophy and disuse atrophy.—We have noticed that the size of an organ in any individual depends on two factors—the minimum standard characteristic of the species and the amount by which this standard is exceeded owing to the functional activity of the organ. In work hypertrophy and disuse atrophy the second factor alone is involved, the specific standard not being altered.

Functional activity of an organ is always associated with increased blood supply. This hyperaemia is not, however, the cause of the hypertrophy. While it is evident that growth cannot occur without increased nutriment, this increased supply will not, of itself, cause growth. Growth is the result of assimilation, and this assimilation is an active process and cannot be induced by an excess of nutriment. On the other hand, a diminution in the supply of nutriment may lead directly to atrophy (starvation atrophy).

In a living organ there are always at work destructive or katabolic processes which result in the formation of products which are either absorbed into the blood or lymph to be ultimately excreted in the form of urea, carbonic acid, etc., or are discharged from the organ by secretion, desquamation, etc. At the same time the organ is always assimilating, that is, it is taking up nutriment from the surrounding medium and building it up into its own substance. In the position of rest there is a balance between these two processes. Under normal conditions any disturbance of this balance is followed by a tendency to return to the original position of equilibrium. If one or the other process predominate the structure diminishes or increases in size, but any such alteration is followed by a compensatory alteration in the opposing process. If, for example, assimilation is in excess the organ increases in size, but there follows an increase in the katabolic processes which thus tends to neutralise the increased assimilation and vice versa. The organ thus tends again to a position of equilibrium.

Now functional activity is always associated with increased katabolism. Hence an organ which is functionally active diminishes, but this diminution is followed by increased assimilation. Hence, on the cessation of the period of functional activity, assimilation is relatively in excess and the organ increases, returning towards the normal. We have seen, however, that living structures display the phenomena of physiological inertia comparable to the ordinary inertia of physics. Hence the organ not only increases until it reaches the size from which it started, but continues increasing for a time so that it becomes larger than it was at first. As the organ increases in size the excess of assimilation over katabolism gradually diminishes and eventually katabolism preponderates so that the organ again diminishes, returning towards the normal. We have thus, following a period of functional activity, first a phase, which we may call

the negative phase, during which the organ is smaller than normal, and secondly a positive phase in which it is larger.

Now if a second period of functional activity occur during the negative phase there will be a second reduction in the size of the organ and, since this period started when the size of the organ had already been reduced, the organ will diminish to a size below that to which it was reduced by the first period. Thus a succession of periods of functional activity, each occurring during a negative phase, will lead to a diminution in the size of the organ. Atrophy from overuse is thus the result of successive periods of functional activity, each occurring during the negative phase, the organ not having time between the periods to regain its original size.

If, on the other hand, the successive periods occur during the positive phase, when the organ is above the original size, each diminution in size due to a period of functional activity will reach to a point which is not so low as the point reached during the previous period. Hence the organ increases in size, and we can say that work hypertrophy is the result of successive periods of functional activity, each occurring during the positive phase, there being time between the periods for the organ to regain and surpass its former size.

Similarly if the functional periods occur just at the time when the organ has regained its original size, the size will remain constant, and lastly, if the periods are at still longer intervals or if no further period of functional activity occur, the organ will continue diminishing in size (atrophy from disuse).

In all these cases the organ tends to a new position of equilibrium in which the size is greater or less than the original size. The "normal" size of any organ is that at which the amount of katabolism during the periods of "normal" functional activity is exactly balanced by the amount of assimilation during the periods of rest. These

observations apply both to organs which have active functions such as secretion or motion and to those of which the function is passive such as resistance to pressure or tension. Structures such as bone or skin submitted to constant pressure undergo atrophy, while if exposed to intermittent pressure they hypertrophy, while if the pressure is removed altogether or is less than normal they again undergo atrophy.

(B) Thus far we have considered hypertrophy as a result of increased functional activity. There are some cases, however, which, while evidently adaptive, arise, not as the result of, but in anticipation of increased functional activity. Such cases are the hypertrophy of the breasts and of the male and female generative organs at puberty ; the hypertrophy of the breasts and uterus during pregnancy ; and the hypertrophy of one testis after the removal of the other. In none of these cases can the hypertrophy be correlated with antecedent hyperergasia, but on the other hand the increased activity follows after the hypertrophy. All these cases have this in common, that the organs involved are concerned, not with the preservation of the individual, but with the continuance of the species. Hence this hypertrophy must be regarded as a character determined by evolution. The mechanism of these changes is not known, but there is evidence to show that the hypertrophy of the breasts during pregnancy is due to chemical substances derived from the foetus and corpus luteum. There is also evidence to show that the hypertrophy of the mucous membrane of the uterus during pregnancy is controlled by the secretion of the corpus luteum.

In these organs we have also a condition of atrophy corresponding to the disuse atrophy of other organs. During the period of sexual activity the female genital organs and the breasts do not atrophy, even although their functional activity is never called into action. After ovulation has ceased, however, when there is no

further possibility of functional activity, the uterus and breasts undergo atrophy.

In all cases of adaptive hypertrophy and atrophy the increase or decrease takes place chiefly in the essential tissue of the organ, the supporting tissues being less affected.

Adaptive hyperplasia.—Corresponding to the hypertrophies in anticipation of increased functional activity, we have adaptive hyperplasia such as is seen in one kidney when the other fails to develop. If one of a pair of organs fails to develop or develops only partially, the other usually shows an increased amount of development, so that the total of the two organs remains about the amount characteristic of the species. This adaptive hyperplasia occurs only during the embryonic period.

Adaptive variations in the proportion of the tissues composing an organ.—Alterations in the proportions of the different tissues composing an organ can only be considered adaptive in the sense that the shape and size of the organ is preserved to some extent. The different tissues cannot replace one another as regards performance of function. These variations occur chiefly in the form of an increase of the supporting tissue to replace a loss of the essential tissue. Hence the condition is known as replacement fibrosis when the fibrous tissue is increased as in cirrhosis of the liver, etc. Also we have replacement gliosis in the central nervous system, and we have replacement adiposis as when an atrophied kidney or muscle is replaced by a mass of fat. Atrophy of the essential tissue is not necessarily accompanied by increase of the supporting tissue. Thus in progressive muscular atrophy we have atrophy of the muscle without an appreciable increase in the fibrous tissue, while in pseudohypertrophic muscular paralysis we have muscular atrophy accompanied by great fibrosis and adiposis, so that the actual bulk of the affected muscles is increased.

In some cases atrophy or hypoplasia of the essential

tissue of an organ is accompanied by dilatation and overgrowth of the blood vessels (angeiectasis).

This group of variations finds its best examples in the central nervous system where atrophy of any of the tracts of fibres is accompanied by a replacement gliosis of the area affected.

Adaptive variations in the structure of tissues. Adaptive metaplasia.—So far we have considered alterations in the size of organs resulting from alterations in the amount of functional activity. We have now to consider the alterations following on a change in the character of the function.

The function of columnar epithelium is to absorb or secrete materials, and it is ill adapted for withstanding friction or pressure. If, now, the conditions are so altered that a surface covered by columnar epithelium is exposed to friction or pressure, we find that it undergoes metaplasia, being transformed into stratified squamous epithelium. The same change occurs rarely in endothelium, e.g. peritoneum. This metaplasia of epithelium occurs especially in chronic inversion of the uterus, in the gall-bladder from the presence of gall-stones, and in the larynx from excessive speaking. In some chronic inflammations a similar change occurs in epithelium. In chronic interstitial pneumonia the endothelium of the pulmonary acini becomes cubical or columnar in shape, and in bronchiectasis and chronic bronchitis the bronchial epithelium may become squamous.

In the supporting tissues we also find metaplasia, as a result of altered function. A tendon is structurally adapted to sustain a strain in the direction of its fibres. If, however, a tendon is subjected to a pressure at right angles to its fibres, we sometimes find that a nodule of bone or cartilage is formed in it, thus adapting it to the new conditions. Examples are seen in the drill bones and cartilages which form in soldiers in the deltoid

tendon from pressure of the rifle, and in the rider's bones which form in the adductor muscles of the thigh owing to pressure in riding.

An interesting example of the adaptation of organs to meet new conditions is seen in the bones. When the direction of the stresses and strains to which a bone is subjected becomes altered, as, for example, in a badly healed fracture or in the deformity produced by rickets, the structure of the bone becomes adjusted to the new conditions by the formation of new bone in the concavity of the deformed bone and the alteration in the position of the bony lamellae of the cancellous tissue. These lamellae shift their position by the addition of new bone on one side, while absorption is taking place on the other.

Other examples of the adjustment of the structure of tissues to meet new conditions are found in the formation of bursae over prominences, in the formation of false joints following ununited fracture, and in the eburnation which takes place in bones which, from destruction of the articular cartilages, are exposed to frictions (arthritis deformans).

These examples of metaplasia and adjustment as a result of new conditions find their analogies in the course of normal development where similar changes occur in anticipation of similar conditions. The epithelium of those parts which will later be exposed to pressure or friction (skin, oesophagus, vocal cords, mouth, vagina, etc.) assumes the stratified squamous type during development. Also where a tendon has to pass round a bony prominence at a considerable angle a sesamoid bone or cartilage is developed in it. The arrangement of the lamellae in cancellous bone is adapted to withstand the strains and stresses to which it will be subjected.

Progressive Variations.

Thus far the variations we have considered are adaptive in character and are hence useful. We have now to

consider variations which do not occur as adaptations but usually arise without definite cause and are harmful rather than useful. Sometimes they may be attributed to a definite exciting cause, but they continue after this cause has ceased to act, and they show no tendency to return to the normal condition. These progressive changes are akin to the tumours which will be discussed later. All the adaptive changes already considered have their counterparts in the progressive changes.

Progressive hyperergasis.—Transient alterations in functional activity are often the result of nervous or emotional causes. Sometimes, however, similar causes may be the starting-point of permanent increase or decrease of functional activity. Examples of progressive hyperergasis may be seen in diabetes insipidus, exophthalmic goitre, etc. Progressive hyperergasis is accompanied by compensatory hypertrophy of the organs affected. Similarly we may have progressive diminution in functional activity. Under one of these two heads we may include many nervous and mental diseases.

Progressive variations in growth.—These differ from the adaptive variations in that they consist in variations in the size of organs above or below the size characteristic of the species and are not dependent on alterations in functional activity.

Progressive atrophy is found especially in the nervous system and muscles (progressive muscular atrophy, primary muscular atrophy). In these conditions the structures waste and their functional activity is correspondingly diminished. Progressive atrophy of the essential tissue of an organ may or may not be accompanied by an increase in the supporting tissue. In progressive hypertrophy and hyperplasia or *gigantism* an organ may increase to a size which is many times the normal. Progressive hypertrophy of the breast, which usually commences at puberty, may continue until the organ becomes of enormous size—up to 20 or 30 pounds in

weight. In the rare condition known as progressive hypertrophic muscular dystrophy, the muscle fibres may be many times the normal size and the bulk of the muscle may be so great as to be a serious inconvenience and to necessitate its removal. There is no increase of functional capacity in the affected muscle. Other examples of progressive hypertrophy are seen in the thyroid (parenchymatous goitre), spleen (splenomegaly), bones (leontiasis ossea), and in the limbs or other parts of the body (local gigantism). The organs which are the seat of progressive hypertrophy may or may not show an increase, and often show a decrease or complete absence, of functional activity.

Enlargement of a structure from diminished waste.—We have seen that in a state of rest there is a balance between the assimilative and katabolic processes. The cases of progressive hypertrophy which we have considered may be attributed to increased assimilation which is not balanced by a corresponding increase in katabolism. We sometimes, however, meet with cases in which the organ increases, not owing to increased assimilation, but from a diminution in the destructive processes. For example, in rodents the incisor teeth continue growing throughout life, this growth being balanced by the constant attrition between opposing teeth. If, however, the teeth are displaced so that they are not in apposition, the attrition is absent and, the growth continuing, the teeth enlarge so as to form what are practically tusks. The teeth, owing to their normally curved shape, grow in the form of a circle, and the enlargement may continue until they penetrate the skull. Again, in the normal skin proliferation is always going on, the increase in the number of cells being balanced by the loss of cells at the free surface by desquamation. If, however, desquamation does not take place owing to an abnormal amount of cohesion in the upper layers, the epidermis becomes thicker as in ichthyosis, cutaneous horns, etc. Similarly nails enlarge

when they are not subjected to the normal amount of wear and tear (onychogryphosis). In animals which are treated with repeated small doses of phosphorus or arsenic the bones become thickened at the expense of the medullary cavity. This seems to be due to a diminution in the amount of bone absorption.

Analogous to these cases are those in which an organ which is fully grown fails to undergo atrophy. The thymus normally undergoes atrophy during childhood, but it may persist into adult life. The uterus also sometimes fails to undergo the normal amount of atrophy after parturition (subinvolution).

Similarly we have analogous alterations in the functional activities of the body. Diminished oxidation as in anaemia or in want of exercise leads to an increase in the amount of stored fat (obesity, fatty changes), and excess of sugar in the blood may be attributed to a deficiency of the normal glycolytic processes.

The alteration in the connective tissue in myxoedema is due to a loss of the normal internal secretion of the thyroid, and it is probable that the increase of connective tissue associated with venous or lymphatic obstruction (elephantiasis, etc.) is due to a diminution in the normal oxidative processes.

Progressive increase of one tissue of an organ.—Some of the cases reported as progressive hypertrophy of the breast are really cases of progressive fibrosis, the increase occurring in the fibrous tissue only. We may also have a progressive fibrosis of nerves, and some of the cases of enlargement of the prostate are due to progressive increase of the fibrous or muscular elements without definite tumour formation. We also have progressive gliosis of the central nervous system (syringomyelia). Some of these conditions will be considered more fully in connection with the corresponding tumours.

Progressive metaplasia.—The best example of progressive metaplasia is found in the rare disease called

myositis ossificans, which is characterised by the progressive ossification of the connective tissue of the muscles. Another example is rheumatoid arthritis in which the primary lesion consists in a conversion of the hyaline articular cartilage into fibrocartilage.

Other examples of one or other of the progressive processes, the pathology of which is imperfectly understood, are leucocythaemia, pernicious anaemia, erythrocythaemia, Hodgkin's disease, diabetes mellitus, etc.

CHAPTER II

REGENERATION, TRANSPLANTATION

WHEN a portion of the body is removed or destroyed by disease it is, under certain circumstances, restored. In so far as the new tissue which takes the place of the old has the same structure and properties as those of the part which was removed, this process is known as *regeneration*.

Regeneration of Organs and Parts of the Body.

In protozoa the whole body can be regenerated from a fragment provided that the fragment contain a portion of the nucleus. In metazoa the capacity for regeneration is more limited, but in several of the lower animals it is still very high. Thus, in the coelenterata (e.g. *Hydra*) the whole body can be regenerated from a small fragment provided that the fragment contain both ectoderm and endoderm. Starfish can reproduce an arm which has been lost, and a single arm can reproduce the whole organism provided that it has a portion of the disc attached to it. In many of the worms, also, the whole organism may be regenerated from a small portion, though this property differs widely in different genera. It is most marked in the planarian worms which may be divided into several pieces, each piece being capable of reproducing a perfect animal. Several of the round worms also show a high degree of regenerative capacity. In the common earthworm the power is more limited. If an earthworm is divided the anterior portion can reproduce a new tail, but the posterior portion can reproduce a head only if the division has been sufficiently far forward.

Proceeding higher up the scale, we find that the power of reproducing the whole organism from an isolated fragment is lost. Regeneration is here limited to the reproduction of limbs and isolated organs. Thus among crustacea crabs can reproduce a limb. These animals possess the power of autotomy, i.e. the power of casting off a limb which has been damaged. This is effected by muscular action which causes the limb to break off at a particular place. A new limb is subsequently developed from the stump. Some insects have this same power of autotomy and subsequent regeneration. Crabs can also reproduce an eye which has been removed provided that the optic ganglion has not been destroyed. Molluscs, again, show a considerable power of regeneration. Snails can reproduce a tentacle with its eye and an octopus can reproduce an arm.

When we come to the vertebrata we find that the capacity for regeneration is still more limited. Apart from the amphioxus the power of reproducing lost parts is greatest in certain amphibia. A newt can reproduce an entire limb or a tail which has been removed, and also an eye, provided that a portion of the eye be left. A frog, however, except in the larval stage, has no such power, the wound being merely closed without the limb being reproduced. Some lizards possess the power of autotomy and reproduction as regards the tail, but cannot reproduce limbs. Birds can reproduce the beak and other parts of the face, but, otherwise, their power of regeneration is very limited. In the mammalia we find that, if we except the normal periodical reproduction of the antlers in stags at the breeding season, the power of reproducing organs and parts of the body is lost altogether in post-natal life.

The process of regeneration in these cases follows, as a rule, very closely the normal process of development. An interesting exception is found in the case of the lens of the eye of the newt, which, if removed or displaced, can be regenerated from the epithelial cells of the iris.

Regeneration of Tissues and Cells.

In man and in the mammalia generally regeneration is limited to the reproduction of tissues and cells and, even then, is usually very imperfect. Throughout life certain tissues are continually being regenerated. In the surface epithelium of the skin and mucous membranes, in the seminal epithelium of the testis, and in the blood-forming organs, new cells are continually being produced to replace those which are lost by desquamation, etc. Similarly the mucous membrane of the uterus is periodically regenerated after the separation in connection with menstruation. In bones, too, new bone is continually being formed by the periosteum. Other tissues such as fibrous tissue, glandular epithelium, and nerve fibres show a considerable capacity for regeneration under certain circumstances. In the regeneration of tissues the new tissues formed are derived from pre-existing tissues of the same kind, whereas in regeneration of organs there is always a formation of new structures from pre-existing structures of a different kind. The former corresponds to growth and the latter to development. ?

Nervous tissue.—If a nerve cell is destroyed it is not regenerated. A few mitoses have been described in the neurocytes in the neighbourhood of a lesion of the central nervous system, but these are apparently imperfect, and do not lead to cell proliferation. On the other hand, damage to a portion of a nerve cell may be repaired. If we adhere to the neuron theory in its simplest form, we must consider the axis cylinder of a nerve fibre as a portion of the nerve cell. If a nerve be completely divided the nerve fibres in the peripheral end degenerate. In the central end there is a slight amount of degeneration of the nerve fibres, but this is followed by regeneration, the fibres growing out from the cut end. If the cut ends of the nerve are widely separated, these fibres growing from the central end become turned back on themselves,

and form a convoluted mass which, together with the cicatricial tissue which is produced at the same time, form a bulbous swelling on the end of the divided nerve—the so-called amputation or traumatic neuroma. If,



FIG. 1.

Bulbous nerve. From an amputation stump. In the upper part of the section is seen the nerve trunk. At the lower end of this the fibres are seen to be passing in all directions and forming, together with the intervening fibrous tissue, the bulbous swelling in which the nerve terminates.

however, the cut ends of the nerve be brought into apposition, the growing nerve fibres of the central end pass into the peripheral end, and may eventually reach their distribution in the muscles, etc., so that function

may be restored. This is not the place to discuss the vexed question whether the regeneration is wholly from the central end or whether it may be partly peripheral in origin. In either case regeneration is complete only if there is continuity between the two ends. While the fibres of a peripheral nerve show a considerable capacity for regeneration, those in the central nervous system are not regenerated.

Striated muscle.—If a wound is made in a muscle the damaged fibres degenerate. The striated substance (myoplasm) disappears and the rest of the fibre—nuclei and sarcoplasm—becomes segregated into numerous cells which undergo proliferation by mitosis. Giant multinucleated cells are also formed by amitotic division of the nuclei. Many of these cells disappear while others remain and elongate, eventually forming new myoplasm and so becoming new striated fibres. Sometimes new fibres are formed by budding from old fibres which have been partially damaged. These newly formed fibres eventually for the most part disappear partly owing to strangulation by the cicatricial tissue which is formed at the same time but chiefly owing to the fact that, having no nervous connections, they are incapable of functional activity.

Smooth muscle.—Smooth muscle shows a slight amount of regenerative capacity, new fibres being produced by mitosis from the old fibres in the neighbourhood.

Fibrous tissue.—This of all tissues shows the greatest regenerative capacity. The healing of every wound depends for the most part on the formation of new fibrous tissue. The regeneration takes place from fibroblasts which are themselves derived from pre-existing fibrocytes by mitosis. The new formed fibrous tissue shows a great tendency to subsequent contraction, thus giving rise to the depression of old scars. This contraction doubtless plays a part in preventing the efficient regeneration of the more essential tissues—muscle, epithelium, etc.

Blood vessels.—Regeneration of blood vessels takes place from the capillary endothelium. This buds outwards, forming long solid processes which join with similar processes from other capillaries. These processes subsequently become hollow. There is thus produced a network of new capillaries. Later on the capillaries may acquire muscular and fibrous coats derived from the arteries and veins with which they are connected.

Cartilage.—Regeneration of cartilage is slow and imperfect. It may occur from the perichondrium or from the chondrocytes. A wound in cartilage is usually filled by fibrous tissue.

Bone.—In the healing of fractures we see evidence of the great regenerative capacity of bone. This regeneration takes place both from the periosteum and from the endosteum. Throughout life bone is constantly being regenerated from these two sources. The whole shaft of a bone may be removed and, if the periosteum be left, it will be regenerated and become of functional utility again. During the healing of a fracture the regenerating bone with the associated fibrous tissue (callus) is, at first, in excess of the amount necessary for the final union of the fragments. Later on the excess is removed by gradual absorption. Cartilage is often found as an intermediate stage of the bone formation.

Surface epithelium.—If some of the epidermis be removed, as in an abrasion or wound, the defect is rapidly covered by new epithelium derived by proliferation from the epithelial cells at the margin of the wound. This regeneration is assisted by the fact that the young epithelial cells have a certain power of amoeboid movement which enables them to spread over the wound to some extent. If any epithelial structures such as hair follicles, sweat glands, etc., remain in the surface of the wound they may act as separate centres of epithelial regeneration. In this regeneration of epidermis accessory structures such as hair follicles, glands, etc., are not

reproduced. The epithelium of mucous membranes is similarly regenerated and, in the stomach and intestines, it may be accompanied by the formation of simple tubular glands such as Lieberkuhn's follicles. The epithelium of the mucous membrane of the uterus is, after menstruation, regenerated from the extremities of the uterine glands, which remain after the exfoliation of the mucous membrane.

Glandular epithelium.—Glandular epithelium shows a



FIG. 2.

Regeneration of epithelium. This is a section of a healing wound from a dog. The dark mass on the surface of the wound is the scab composed of fibrin and leucocytes. The epidermis is seen to be growing under the scab from the right side. The lower surface of the growing edge of the epithelium where it rests on the subjacent granulation tissue is irregular.

much less regenerative power than surface epithelium. While all glands show a certain capacity for regeneration, this is, as a rule, very limited and of little or no functional utility. Thus after a wound of the kidney the collecting tubes may show some evidence of regeneration, but functional urinary tubes are not formed. It is a general rule that in glands the ducts have a greater regenerative

capacity than the secreting epithelium. The duct epithelium, however, retains its characters and does not give rise to secreting epithelium. In the liver there is a considerable power of regeneration. In the scar of a wound there may be found new-formed bile ducts and groups of liver cells. Regeneration is most marked, however, in cases of destruction of the hepatic tissue by disease such as acute yellow atrophy or cirrhosis. Under these conditions considerable nodules and masses of newly formed hepatic tissue may be formed, and these nodules may be of functional utility. The thyroid is also capable of a functionally useful regeneration.

Blood.—The blood is a secretion rather than a tissue. Hence its regeneration differs from the regeneration of tissues and depends on increased functional activity of the blood-forming organs. After a single considerable haemorrhage the volume of the blood is first restored by the entrance into the circulation of tissue lymph and by increased absorption of fluid from the alimentary canal. The effect of this is to make the blood abnormally dilute. The number of corpuscles is restored later by hyperergasia of the bone marrow. The process is the same as is constantly going on in normal conditions but is more rapid, and immature cells such as nucleated erythrocytes, and myelocytes may appear in the circulation. The mechanism of this process is unknown since we do not know the mechanism by which the normal composition of the blood is regulated. The regulation is probably effected by hormones.

We thus see that it is only in a few cases that regeneration in man and in the mammalia generally is of functional utility. Regeneration of nerve fibres in divided nerves is functionally useful if the regenerating fibres find their way into the distal end of the nerve, and so to its termination. Regeneration of surface epithelium, of the blood, and of supporting structures such as bone and fibrous tissue is also of functional utility. Regeneration of

striated muscle is of little or no utility since the newly formed fibres have no nervous connections. Probably only in the case of a partially damaged fibre which retains its nervous connection is any functional activity possible in the regenerated muscle. Similarly in the case of glands the regenerated tissue may be derived all from the ducts or all from the secreting epithelium or partly from both sources, but the definite relations of the secreting epithelium to the ducts, blood vessels, nerves, etc., which is necessary for functional activity is not, as a rule, restored. It is possible that in some cases of acute yellow atrophy of the liver where the stroma is not affected and where some of the cells of a lobule have escaped destruction, the lobule may be restored so as to be functionally useful, since here it is possible that the necessary relationship between the secreting cells, the ducts, the blood vessels, and the nerves may be restored. In the case of ductless glands it is possible for the regenerated tissue to be functionally useful.

On the whole, therefore, comparing compensatory hypertrophy with regeneration, we find that the former is the more important process, as in it the normal arrangements of the organ as to vascularisation and nervous connections are unaltered, whereas in regeneration these arrangements are not reproduced.

We may sum up the conditions of regeneration as follows :

1. In the higher animals regeneration of a particular tissue always proceeds from a tissue of the same kind or from a closely related tissue. Thus epithelium is always regenerated from epithelium and muscle from muscle. Hence it follows that—

2. Regeneration is impossible unless some of the same type of tissue is present in the neighbourhood of the lesion. A kidney which is completely removed is not regenerated nor is a bone if the whole bone with its periosteum has been removed.

3. Phylogenetically regeneration is more complete the lower the animal in the animal kingdom. In the lower animals there may be regeneration of organs or of parts of the body, while in the higher animals the power is limited to the restoration of lost tissues. The position in the animal kingdom is not, however, the only factor which determines the amount of regenerative capacity, since closely allied species may show widely different powers of regeneration.

4. Ontogenetically regeneration is more complete the younger the animal. It is greatest in the segmenting ovum and diminishes as development proceeds. Thus a single blastomere in the two-celled stage of a frog's ovum gives rise to a half embryo from which the missing half may be subsequently regenerated. A tadpole has a considerable power of regeneration, while a frog displays very little.

5. In any animal, the greater the liability of any part to injury, the greater its power of regeneration.

6. Regenerated tissue is permanent only if it be capable of functional activity.

Transplantation and Grafting.

If an organ or piece of tissue be partially severed from its connections and moved so as to occupy a new position it will, in many cases, form connections with the adjacent tissues, and it will continue to grow and perform its function in its new position. This is known as *transplantation*. Again, if an organ or piece of tissue be completely severed from its connections and placed in a new position in the same body or in the body of another animal of the same species, it may form connections in its new position and continue to live and perform function. This is known as *grafting*.

Transplantation is employed practically in plastic operations in which flaps of skin or mucous membrane are partially separated and shifted so as to cover raw surfaces or to remedy deformities. Examples are seen in the

operations for cleft palate and hare-lip and in the filling up of large operation wounds by shifting flaps of the neighbouring skin. Transplantation is also employed in uniting nerves which have been divided into the trunks of other nerves. Tendons also are sometimes transplanted or their attachments may be shifted.

The phenomena of grafting have a greater pathological interest. A vast amount of experimental work has been performed in this connection. Pieces of every kind of tissue have been removed from an animal and have been placed in the blood vessels, serous cavities, subcutaneous tissue, etc., of the same animal or of other animals of the same or different species. The results of these experiments have shown the following facts :

1. The fate of the graft varies. In some cases the graft is rapidly absorbed. In most cases the graft survives for some time, and may show a considerable amount of growth, but, sooner or later, the growth ceases and the graft is gradually absorbed. In other cases, again, the graft may be permanent and functionally useful.

2. Grafting is most successful when the graft is transferred to another part of the individual from which it was taken. It is also successful when it is transferred to another individual of the same species. Between animals of different but allied species grafting is hardly at all possible, and it fails altogether when the graft is transferred to an animal of a different genus.

3. Grafting is more successful in the lower animals. In some of the invertebrata and in tadpoles large portions of the body may be successfully grafted on to another animal.

4. In the same species grafting is more successful the younger the animal. This applies both to the animal from which the graft is taken and to that to which it is transferred.

5. Success in grafting depends to some extent on the size of the graft. A small portion of tissue is more likely to

survive than a large portion. In all grafts a large portion undergoes necrosis, the surviving portions being those which, being at the periphery of the graft, are nearest to the surrounding tissues from which the nutriment is derived.

6. A tissue which is capable of continuing its functional activity in the new situation is more likely to survive than one which is incapable of doing so. Epithelium introduced into a vein may grow for a time, but is sooner or later absorbed, while the same epithelium grafted on a raw surface will produce a permanent covering layer of epithelium. A graft of striated muscle is usually absorbed rapidly. If, however, the graft is stimulated electrically at regular intervals, the graft may survive and may even increase in size. On the cessation of the stimulation the graft ceases to grow and is eventually absorbed.

Recently it has been found that by taking suitable precautions it is possible to succeed with large grafts, even whole organs being grafted successfully. A kidney can be transferred from one animal to another from which the corresponding kidney has been removed, and, if care be taken to restore the circulation by joining the arteries and veins of the graft to the corresponding vessels in the second animals, and if the ureter of the grafted kidney be connected to the bladder, the grafted kidney may survive and perform its function in its new situation. Similarly bones and joints may be grafted.

7. Grafting is most successful if the transference is made immediately. It may, however, be successful in some cases if the graft has been kept outside the body under suitable conditions for some days or even weeks.

Bone.—If periosteum be grafted into a situation from which a piece of bone has been removed, it may survive and produce new bone which may become functionally useful. If a portion of bone including the periosteum be grafted into a defect in another bone, the grafted bone

dies. The periosteum, however, survives and produces new bone which gradually replaces the dead bone as the latter is absorbed. The grafted bone, although it dies, yet serves a useful purpose in acting as a scaffolding on which the new bone may be laid down.

Ductless glands.—The thyroid can be successfully grafted into the subcutaneous tissue and, although a large portion may die, yet the part of the graft which survives may undergo hypertrophy and continue to be of functional utility. Similarly ovaries may be grafted into other positions in the abdominal cavity. The pancreas may be grafted into the connective tissue and may continue to supply its internal secretion in its new situation. Removal of the pancreas in dogs is followed by glycosuria. This, however, does not supervene if a portion of the pancreas be grafted into the connective tissue.

Skin.—The most important example of grafting is skin grafting, which is employed to accelerate the healing of ulcers and other raw surfaces. We have seen that a raw surface becomes covered with epidermis derived from the epidermal cells at the margin of the wound. If, however, the raw surface is of large extent, this process of healing is very slow. If, now, we place on the surface portions of epidermis derived from other parts of the body, these portions become adherent and form new centres of epithelial proliferation so that the covering of the wound with epidermis is thereby hastened. The grafts must include some of the basal layer of epithelial cells. Success is most certain when recent grafts are used, but they have been kept for days or weeks and have even been dried, and yet have been grafted successfully. When the graft is applied to the granulating surface it adheres by the coagulation of the lymph with which the surface is covered. This layer of coagulated lymph then becomes vascularised, and so the nutrition of the graft is maintained and a perfect union is effected. The greater number of cells in the graft die, but some of the deeper cells survive

and proliferate, thus forming new foci from which epithelium may spread over the wound.

Implantation Cysts.

If, instead of being placed on a raw surface, epidermis be grafted or transplanted into the connective tissue, it will grow in the new situation, spreading out laterally until it forms a complete lining to the cavity produced by its introduction. The epithelium will subsequently continue to proliferate just as it does on the surface of the skin, and the old cells will be thrown off into the cavity of the cyst, which will thereby become distended. There is thus produced a cyst lined by squamous epithelium containing a semi-solid substance formed by degeneration of the desquamated cells. Such cysts are not only the result of experimentation, but they may also occur as the results of accidents, and are then called traumatic or implantation cysts. They may be found in the fingers as the result of a prick with a needle carrying some of the epidermis into the subjacent tissue. Sometimes they are found in the iris owing to a foreign body which has penetrated the cornea, carrying with it some of the corneal or conjunctival epithelium.

Sequestration Cysts.

Exactly similar cysts are met with arising spontaneously as the result of errors of development. They are due to the dislocation of epithelial rudiments into the connective tissue during development, and are known as sequestration cysts. The most common situation is in the connective tissue of the head and neck in situations corresponding to the branchial clefts or the lines of union of the various processes which form the face. If these cysts have a lining of simple epidermis they are called epidermoid cysts. If, in addition, they contain hair follicles and cutaneous glands, they are known as dermoid cysts. Similar cysts arising in connection with the branchial clefts may be lined with mucous membrane derived

from the primitive pharynx. Such cysts are known as mucosal cysts, and the lining epithelium may be squamous or columnar (ciliated). Sequestration cysts may also occur in connection with the intestines, where they are



FIG. 3.

Sequestration cyst. Breast. This is an epidermoid cyst as it contains no accessory structures such as hair follicles or sebaceous glands. The cavity of the cyst is above and is filled with layers of desquamated horny epithelium. The lining of the cyst consists of a uniform stratified squamous epithelium resembling epidermis.

known as enterocystomata. They have a lining resembling the intestinal mucosa.

Sequestration dermoids and epidermoids are also found in deeper positions such as in the skull, thorax, abdomen, etc. These cysts occurring in the cranial cavity form the peculiar structures known as cholesteatomata, which are cysts lined with squamous epithelium and filled with desquamated keratinised cells. The contents of such cysts contain crystals of cholesterin, and have a peculiar pearly lustre. Cholesteatomata are also found in the middle ear and occasionally in other situations.

CHAPTER III

TUMOURS. INTRODUCTION

IN discussing hypertrophy we have seen that there are conditions known as "progressive hypertrophy," in which there is a hypertrophy of the whole organ beyond the needs of the organism. There are also conditions in which the supporting tissue of the organ shows a similar progressive increase. In both these cases there is a more or less symmetrical enlargement of the whole organ or of a large part of it.

We now have to deal with new formations which, while showing a similar progressive growth, are strictly localised to some part of an organ, the rest being primarily unaffected. Such localised new formations are called *tumours*.

A tumour may be defined as *a mass of cells, tissues or organs resembling those normally present in the body, but arranged atypically, which grows at the expense of the body, without subserving any useful purpose therein.*

For example, we may find a new formation characterised by the presence of squamous epithelial cells lying in the subcutaneous connective tissue spaces instead of forming a definite epithelium covering the surface. Again, we may find a mass of fibrous tissue not forming a definite structure such as a tendon or fascia. Lastly, we may find a mass containing organs such as skin, glands, teeth, ganglia, etc., arranged irregularly. Such new formations, if they show signs of progressive growth, are "tumours."

In inflammatory conditions also we find localised

increased formations of tissues, but in this case the increase is the result of a reaction, protective and therefore useful in character, against an irritant. Such masses are excluded from the category of tumours. Such inflammatory masses are seen in the encapsulation of foreign bodies, in the infective granulomata, in the callus formed at the seat of a fracture and in granulation tissue generally. In these conditions, if we can remove the source of irritation, the process comes to an end and the excess of tissue is absorbed.

It is apparent from the above definition that tumours are closely allied to malformations and, indeed, it is sometimes difficult to decide what is a tumour and what a malformation. We must here apply the criterion of progressive growth. If, for instance, we find a nodule of cartilage embedded in the substance of an adult bone we call it a malformation. If, on the other hand, we find in a similar situation a mass of cartilage which grows and displaces the parts around it we call it a tumour. In fact, as we shall see later, tumours often grow from malformations.

When we are discussing any series of phenomena, it is useful to adopt some method of classification. The classification of tumours adopted here is based on the different orders of units of organisation—organs, tissues, cells. In the first place we have tumours characterised by the presence of organs—skin, teeth, glands, etc.—arranged atypically. These are called organ tumours or *organomata*. In the next place we have tumours characterised throughout by the presence of tissues arranged atypically. These are called tissue tumours or *histiomata*. Lastly, we have tumours characterised by the presence of cells arranged atypically. These are called cell tumours or *cytomata*. The last two classes are subdivided according to the different kinds of tissues or cells respectively. The classification is therefore as in the accompanying table.

CLASSIFICATION OF TUMOURS

A. ORGANOMATA, or Organ Tumours.

1. Teratoma^{ata}

B. HISTIOMATA, or Tissue Tumours.

a. DESMOMATA, or Supporting Tissue Tumours.

- | | |
|---------------|---------------------|
| 1. Myxoma | Mucous tissue. |
| 2. Fibroma. | Fibrous tissue. |
| 3. Lipoma. | Fat. |
| 4. Chondroma. | Cartilage. |
| 5. Chordoma. | Notochordal tissue. |
| 6. Osteoma. | Bone. |
| 7. Odontoma. | Dentine. |
| 8. Glioma. | Neuroglia. |

b. NEUROMATA, or Nerve Tumours.

- | | |
|-------------|-----------------|
| 1. Neuroma. | Nervous tissue. |
|-------------|-----------------|

c. MYOMATA, or Muscle Tumours.

- | | |
|-----------------|------------------|
| 1. Rhabdomyoma. | Striated muscle. |
| 3. Leiomyoma. | Smooth muscle. |

d. LYMPHOMATA, or Lymphoid Tissue Tumours.

- | | |
|--------------|------------------|
| 1. Lymphoma. | Lymphoid tissue. |
| 2. Myeloma. | Bone marrow. |

e. EPITHELIAL and ENDOTHELIAL HISTIOMATA.

Papilloma, Adenoma, Angelioma.

C. CYTOMATA, or Cell Tumours.

- | | |
|-------------------------------|--|
| a. BLASTOCYTOMATA. | Indifferent cells. |
| b. SARCOMATA (DESMOCYTOMATA). | Supporting tissue cells. |
| c. NEUROCYTOMATA. | Nerve cells. |
| d. MYOCYTOMATA. | Muscle cells. |
| e. LYMPHOCYTOMATA. | Lymphoid cells. |
| f. CARCINOMATA. | Epithelial and endo-
thelial cells. |

This classification will be found useful for practical purposes. Each group and each individual kind of tumour has certain peculiarities of structure or character which separate it from other groups or individual tumours. We must remember, however, that the individual tumours in this classification are types only. Intermediate and compound tumours exist. Thus we may have a tumour characterised by the presence of fibrous tissue and mucous tissue, or of fibrous tissue and bone, etc. We may also

have cell tumours in which definite tissues such as cartilage may be found. On the whole, however, the type tumours are the commoner, and the characters of the intermediate or compound tumours are intermediate between the characters of the type tumours of the elements of which they are composed.

As regards nomenclature, the organomata are called teratomata from their resemblance to monsters (Gr. *τέρας*, a monster). The histiomata are named from the tissue which forms the characteristic feature of their structure with the addition of the termination *oma*. This, however, is not the case with the epithelial and endothelial histiomata because the terms "epithelioma" and "endothelioma" are sometimes applied to certain forms of cytomata. The cytomata are properly named from the cells which form their characteristic elements. Epithelial cytomata are, however, called by the old Greek name carcinoma (*καρκίνωμα*, *καρκίνος*, a crab) from the supposed resemblance of these tumours to a crab (Lat. cancer). Supporting tissue cell tumours (desmocyotomata) are named sarcomata (Gr. *σάρκωμα*, a fleshy mass). Collectively the cytomata are called cancers. Compound tumours are named by compound words representing the various constituents of the tumours: hence myxofibroma, osteofibroma, chondrosarcoma, etc.

In assigning a place in this classification to any given tumour, we are guided by the histological structure. If we find definite organs such as skin, teeth, etc., we call it an organoma. If the tumour is wholly composed of definite tissues not arranged in the form of organs, it is a histioma, while if it is composed, wholly or in part, of cells arranged irregularly and not forming definite tissues, it is a cytoma. If, for instance, we find a tumour composed of epithelial tubes embedded in connective tissue, the epithelial cells everywhere forming a definite membrane lining the tubes, or, in other words, if in all parts of the tumour the epithelial cells form a definite epithelium,

the tumour is an epithelial histioma. If, on the other hand, we find in some parts of the tumour the epithelial cells not forming a definite epithelium, but lying irregularly in spaces in the fibrous tissue, the tumour is an epithelial cytoma (carcinoma). Again, if the tumour is composed throughout of definite fibrous tissue in which each cell is separated from the neighbouring cells by intervening fibres, the tumour is a fibroma. If, however, it is com-



FIG. 4.

Tissue tumour. Fibroma. This is from a large solitary fibroma of the sciatic nerve. It consists of ordinary dense fibrous tissue resembling tendon. There are few nuclei and distinct wavy fibres. See also fig. 10. Contrast with fig. 5.

posed, wholly or in part, of similar cells separated by a minute amount of intercellular substance not forming definite fibres, the tumour is a sarcoma.

The recognition of the different types of the histiomata offers, as a rule, little difficulty. With the cytomata the difficulty of diagnosis is considerably greater. This arises from the fact that the different cell-types are almost entirely distinguished by the characters of the tissues of which they form part, e.g. a fat cell is not recognisable

apart from its contained fat, and a cartilage cell is distinguished by the formation of the cartilaginous intercellular substance. Apart from these characters, cells of widely different nature may closely resemble one

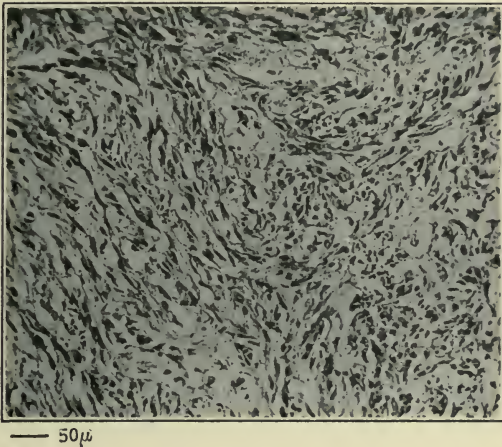


FIG. 5.

Cell tumour. Spindle-celled sarcoma of the stomach. This is composed entirely of spindle-shaped cells with a scanty amount of intercellular substance. The cells show no definite arrangement. Contrast with fig. 4. See also fig. 44.

another. Hence in the purely cellular cytomata it may be impossible to decide on the nature of the constituent cells. We cannot, for instance, recognise an indifferent cell as such. We can only recognise such cells by the fact that they give rise to differentiated cells and tissues of various kinds. Again, it is not always possible to decide whether a tumour is composed of supporting tissue cells (desmocytes) or of epithelial cells, i.e. whether it is a sarcoma or carcinoma. The difficulty is greatest in regard to the endothelial cytomata. Morphologically, endothelium is a variety of epithelium, both being membranes composed of cells in contact with one another, and in accordance with this fact many of the cytomata of

endothelial origin are not to be distinguished from similar tumours arising from other kinds of epithelium. Under various pathological conditions endothelial cells are apt to assume the characters of other kinds of epithelium. On the other hand, endothelial cells sometimes closely resemble supporting tissue cells. In cases in which there is a difficulty in allotting a given tumour its proper place in the classification, it may be necessary to examine sections from a number of different parts of the tumour before coming to a definite conclusion.

Multiple Tumours.

It is not infrequent to find several tumours occurring either simultaneously or in succession. This multiplicity may arise in different ways. In the first place there may be two or more tumours of the same or different types occurring quite independently of each other. Thus we may find in the same patient an adenoma of the breast and an ovarian cyst, or we may find myoma and carcinoma of the uterus. Occasionally tumours of different types may occur in such close proximity as to form a combined tumour. Such tumours differ in no respect from similar growths occurring singly. In the second place we may have several tumours—sometimes hundreds—occurring simultaneously in a single organ or system of organs, e.g. skin, uterus, nerves, bones. Such tumours are all of the same or closely allied types. Thus v. Recklinghausen's disease is characterised by a large number of fibromata of the nerves and skin. Sometimes a few of the tumours may show the characters of a myxoma or sarcoma. In these cases of multiple tumours there is usually a more or less symmetrical distribution of the tumours. Lastly, multiple tumours may arise secondarily as a sequel to a single primary growth from which they are directly derived. They arise in different organs such as lymph glands, lungs, liver, etc., and show the same histological characters as the primary. This phenomenon

is known as metastasis, and the secondary tumours as metastatic tumours. Tumours which give rise to metastasis are almost invariably cytomata.

Clinically tumours are classed as *benign* and *malignant* according to the effects they produce on the body. A benign tumour affects the organism merely by the pressure effects produced by its growth, while a malignant tumour, besides these pressure effects, infiltrates and destroys neighbouring structures and gives rise to metastases. We shall discuss the phenomena of metastasis and malignancy more fully in future chapters.

Tumours in Animals.

All kinds of tumours have been described in animals other than man, and tumours of one kind or another have been found in all classes of vertebrate animals and in some of the invertebrata. The anatomical and physiological characters of tumours in animals are identical with the characters of the corresponding tumours in man allowing for differences of structure in different animals. For instance, teratomata in birds are similar to teratomata in man, but they contain feathers instead of hairs and, in other animals, teratomata contain the type of hair which is characteristic of the species.

Most of our knowledge of tumours in animals is derived from domesticated races. This is natural, because such animals come more frequently under observation. Tumours do occur in wild animals, but apparently they are more infrequent than those of the domesticated animals. Among domestic animals carcinoma is relatively more frequent in dogs, cats and horses, while sarcoma is relatively common in cattle, pigs, and goats. This difference is probably apparent only in that the latter animals are killed for food, while still young, and carcinoma, which, as we shall see, is a disease of advanced age, is in consequence rarely met with. Carcinoma in cattle is more frequently found in those countries where cattle are used

for draught purposes and where, in consequence, there are more cattle of advanced age. Melanotic tumours are not infrequent in horses and lymphocytomata are found especially in swine. Carcinomata and other tumours are also found in birds (fowls) and in sea and fresh-water fishes.

The fact that tumours occur in animals, and that such tumours resemble those occurring in man, is of the greatest importance, since it has widened the scope of investigation into this branch of pathology by enabling us to supplement the knowledge gained from observation in man by the facts obtained by experiments in animals. Tumours in animals, especially sarcomata and carcinomata, are often capable of being grafted from one animal to another. Hence we are enabled to study the growth and other properties of tumours by experimental grafting. Such grafting is possible only between animals of the same species, attempts at grafting tumours arising in one animal into an animal of another species uniformly proving unsuccessful. This experimental study of cancer has led to important results which have added facts which were not attainable by observation alone. In these investigations mice and rats have been most extensively used. Carcinoma is found more frequently in tame mice than in any other animal. It is not so common in wild mice. Tame rats also suffer from carcinoma and sarcoma. Dogs, too, have been used especially in connection with a peculiar tumour of the genital organs. This tumour has the structure of a lymphocytoma, and forms masses on the penis and in the vulva and vagina, and the disease is transmitted naturally during coitus. It differs from most tumours in being highly contagious and, indeed, it may occur as a serious epizootic.

CHAPTER IV

ORGANOMATA

It is not possible satisfactorily to subdivide the organomata into different groups. The number of organs which can be recognised in a single tumour is usually great, and there is no sufficient basis for subdivision. They are therefore described together under the name *teratoma*.

Teratoma.

A teratoma is a tumour in which we can recognise definite organs which are not arranged so as to form a definite organism or part of the body. We find skin, glands, mucous membrane, teeth, bones, ganglia, nerves, etc., arranged in an atypical manner. In these teratomata we are on the border-line between malformations and tumours. Some of them undoubtedly have an independent growth, and are true tumours, and these shade gradually into what must be considered as malformations. We may have malformations due to the inclusion of one foetus in another—*foetus in foetu*—while, on the other hand, we may have simple cysts lined with true skin—*sequestration cysts*—which (p. 34) are attributable to the sequestration of portions of skin during development. Between these two forms of malformation we have masses of varying degrees of complexity which show a greater or less degree of independent growth in which we find definite organs arranged atypically. These are the teratomata. While the malformations are always congenital, teratomata may arise at any age.

Teratomata may be either cystic or solid, but the two

forms do not differ essentially from one another. Solid teratomata always contain cysts, and the cystic form is due to the enlargement of one cyst out of proportion to the rest of the growth. Teratomatous cysts occur most frequently in the ovary, more rarely in the testis and other situations, and are often called "*dermoid cysts*," since the cyst, which is partly or wholly lined with skin, is the most prominent feature. They, however, always contain other organs besides skin, and hence the term "*teratomatous cyst*" or "*cystic teratoma*" is preferable.

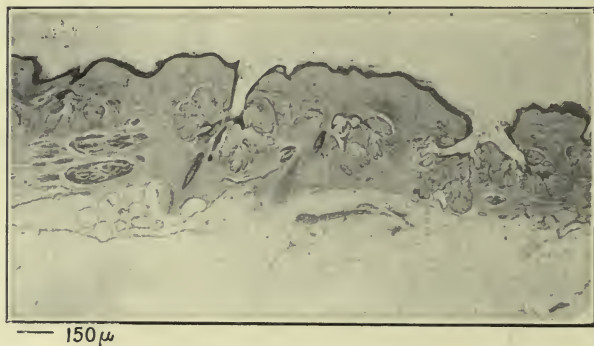


FIG. 6.

Skin from a cystic teratoma of the ovary. This shows the structure of normal skin with hair follicles and very large sebaceous glands. Below and to the left is seen a sweat gland lying in the subcutaneous fat.

A teratomatous cyst presents itself as a cavity, the contents of which resemble soft putty and are composed of desquamated epithelial cells, fats, cholesterin, etc. Such cysts always contain hairs which may be free or may be attached to the cyst wall. These hairs may be several feet in length. On clearing out the contents of the cyst, there will be found a protuberance at one part of the wall projecting into the cavity. This protuberance may be small or large. It is covered by typical skin with very large sebaceous glands,

sweat glands, hair follicles, etc. Teeth are often present singly or in large numbers, and may be fixed in a bone or may simply project from the soft tissues. In the protuberance will be found bones, pieces of stomach or intestines showing typical mucous and muscular coats; brain, sometimes showing convolutions and covered with pia mater; nerves; ganglia; arteries and veins; mammary glands; mucous glands; bronchi; thyroid; lymph follicles; masses of striated and smooth muscle; spaces lined with pigmented epithelium which are

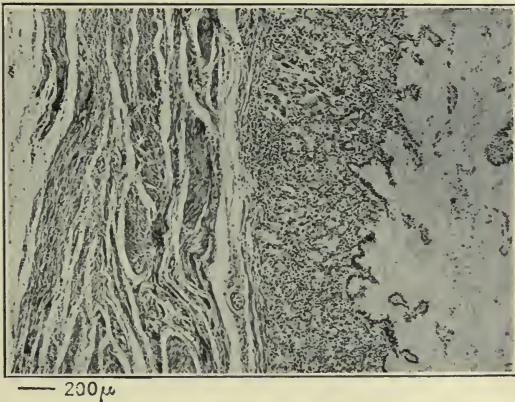


FIG. 7.

Stomach from a cystic teratoma of the ovary. The mucous membrane (to the right), submucous and muscular coats (to the left) can be distinguished. The mucous membrane bears a close resemblance to the normal gastric mucosa.

supposed to represent retina. Apparently there are never found heart, liver, kidney, or genital glands. The existence of lungs is doubtful, and cardiac muscle has been only once described. In most cases a large number of these organs occur together, but one or more may be absent. The cyst, apart from the protuberance, may be lined with squamous epithelium with, or without, hair follicles and cutaneous glands, or it may be lined by a simple columnar or cubical epithelium, or it may be

formed of granulation tissue without an epithelial lining. In the latter case hairs may be found which have been partially embedded in the granulation tissue and are surrounded by foreign-body giant cells.

In some teratomata we may find several cysts of approximately equal size. At least one of these will show a lining of skin while others may be lined with mucous membrane or brain substance. The more solid teratomata show numerous small cysts which are lined with

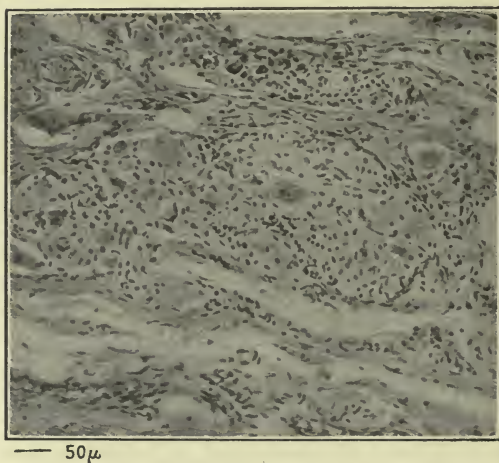


FIG. 8.

Ganglion from a cystic teratoma of the ovary. Several nerve cells can be seen embedded in nucleated fibrous tissue.

skin, mucous membrane, or brain substance, separated by fibrous tissue which may contain cartilage, bone, muscle, and nerves.

Teratomata are found especially in the testis and ovary, the solid forms being commoner in the former and the cystic forms in the latter. They are also found in the pharynx, sacro-coccygeal region and thoracic and abdominal cavities. They are more rarely found in the cranial cavity. Ovarian teratomata may be multiple,

as many as five having been found in a single ovary. Their nature is discussed below (p. 145).

There is a kind of tumour, found especially in the testis, in which there are no definite organs, but merely a number of cysts lined with simple epithelium separated by fibrous tissue in which may be found muscle, cartilage or bone. Such tumours shade gradually into the true teratomata, and may be called "*teratoid histiomata*."

CHAPTER V

HISTIOMATA

THE histiomata are tumours composed throughout of tissues which are not arranged so as to form organs. No tumour, except, perhaps, in the very earliest stages, is composed of a single tissue only, since the presence of supporting tissue and blood vessels is essential to its growth. As a rule, however, one tissue predominates and gives the character to the tumour, the other tissues present being of subsidiary importance. Hence the histiomata are subdivided according to the tissue which forms the dominant feature of the tumour.

(a) *Desmomata.*

The desmomata are connective-tissue tumours, and are subdivided according to the nature of the tissue of which they are composed. With the exception of the specialised supporting tissues neuroglia and notochordal tissue, all the kinds of supporting tissues are interchangeable by metaplasia. Thus cartilage can change into mucous tissue, and fibrous tissue into bone, etc. Hence it is not to be expected that the tumours composed of these tissues should be sharply marked off into different types. As a matter of fact, however, the type forms of tumours corresponding to the types of supporting tissue are the commoner, and hence can be separately described with advantage.

Myxoma.

The myxoma is a tumour composed of mucous tissue, a tissue of the same nature as the connective tissue of the

embryo and of the umbilical cord and vitreous humour. It is a soft elastic tumour which may be lobulated. On section it is found to have a gelatinous, semifluid consistency and a translucent appearance. It may be homogeneous throughout, or may show subdivision into more or less defined lobules by fibrous tissue septa. It contains a large amount of mucin.

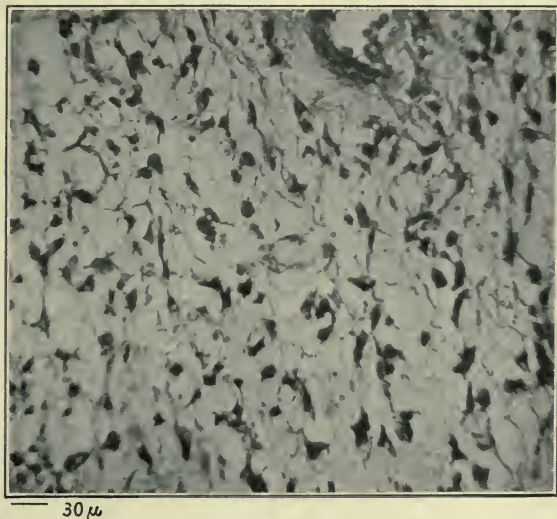


FIG. 9.

Myxoma. Bladder. This consists entirely of a network of delicate branching cells. Appropriate stains show the presence of mucin in the intercellular substance. Above is seen a blood vessel.

Microscopically it consists of cells which have very long tortuous processes which interlace with each other, forming a kind of network, the meshes of which are occupied by a homogeneous intercellular substance which contains mucin as shown by its staining reactions (e.g. it stains purple with thionin or toluidin blue). In this intercellular substance there are delicate fibrillae. In hardened preparations the intercellular substance

may have a granular or stringy appearance. Blood vessels are numerous, the larger vessels being contained in fibrous tissue trabeculae, and the smaller capillaries being found in the intercellular substance. Around the blood vessels are often groups of lymphoid cells, and mast cells and other wandering cells may be found scattered through the tumour in considerable numbers.

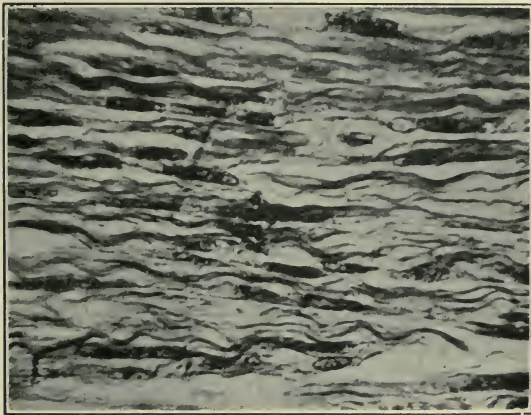
The cells of a myxoma often contain minute globules of fat. Sometimes the fat accumulates to such an extent that the cells come to resemble fat cells, in which case we speak of a *myxolipoma*. In other cases we have an increased number of intercellular fibrils with the formation of fibrous tissue—*myxofibroma*—or the intercellular substance may assume cartilaginous characters—*myxochondroma*.

Myxomata occur in the subcutaneous and subserous connective tissue, in muscles and intermuscular fasciae, in bones, heart, bladder, and nerves. The common mucous polypi of the nose and uterus are, as a rule, not true myxomata, but more strictly oedematous fibromata or an oedematous condition of the mucous membrane with, or without, a mucoid change.

Fibroma.

A fibroma is a mass of fibrous tissue which is not arranged so as to form a tendon or fascia. It is a round or oval tumour, sometimes lobulated. Fibromata may be of any size, some being microscopic while others may form a mass of many pounds weight. The consistency varies according to the structure, in the same way as the consistency of normal fibrous tissue varies. We may have hard fibromata in which the structure is dense like a tendon, or we may have soft fibromata in which the structure is loose like areolar tissue. There is, however, no sharp distinction between the two forms as there are all intermediate grades, and a single tumour may be soft in one place and hard in another. When a hard fibroma

is cut it grates under the knife like a tendon or ligament. The cut surface is grey or yellow in colour and glistening in appearance. Strands of dense fibrous tissue are seen passing in all directions interlacing one another. When a soft fibroma is cut the surface of the section is soft and moist and almost gelatinous in appearance. The softer forms are hardly to be distinguished from myxomata. A typical fibroma is completely encapsulated, and is only



— 45 μ .

FIG. 10.

Fibroma. This is from a large solitary tumour of the sciatic nerve. It is composed of dense fibrous tissue resembling tendon. The wavy fibres are very prominent and the cells few. See also fig. 4. Compare with figs. 11, 12.

connected to the surrounding structures by the blood vessels which enter it on all sides. Some, however, are at one or more points in direct continuity with the surrounding fibrous tissue. This is the case especially in the multiple fibromata of the skin and nerves.

Microscopically the hard fibromata are composed of fibrous tissue resembling tendon in which the intercellular fibres are thick and prominent and the cells compressed between the fibres. Blood vessels are somewhat scarce.

In the soft fibromata the whole structure is looser, the fibres forming a loose network, and the cells, which are spindle-shaped or stellate, being relatively numerous and conspicuous. The tissue spaces may be distended with fluid—oedematous fibroma—so that the tumour more or less resembles a myxoma. Fibromata usually contain elastic fibres in varying amount.

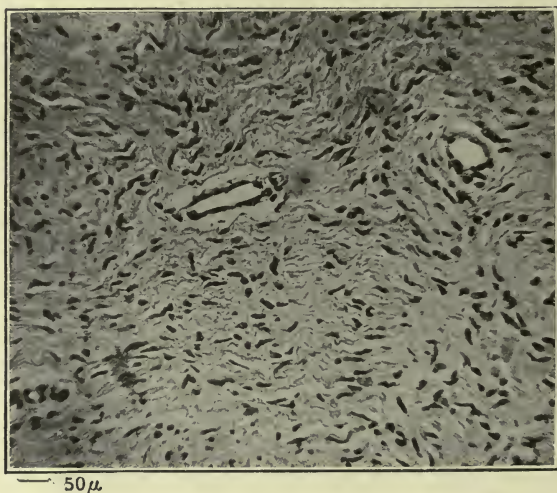


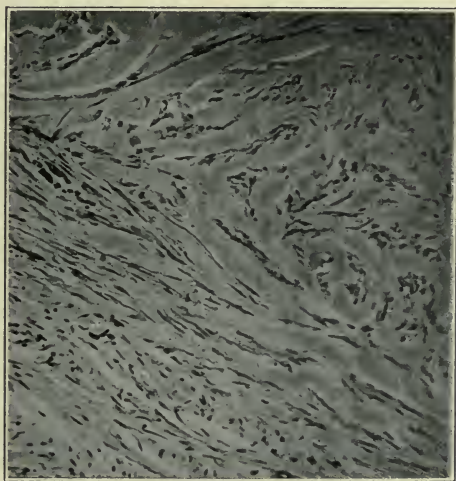
FIG. II.

Fibroma. Skin. From a case of general neurofibromatosis. This consists of comparatively loose connective tissue. In the patient from whom this was taken there were several hundred cutaneous and subcutaneous tumours and some along the nerve trunks. Two well-formed blood vessels are seen in the tumour. Compare figs. 4, 10.

Fibromata may occur in any part of the body. They are most frequently found in connection with the skin, subcutaneous tissue, bones, periosteum, muscles, nerves, tendons and fasciae and larynx. They are less frequent in the alimentary canal and glandular organs. We may notice a few special forms.

1. *Keloid* (Gr. κηλη, a tumour, or κηλís, blemish).—

A keloid is a hypertrophic condition of a scar. In some cases it appears to arise independently of any injury, but the injury may be very slight, and hence may be overlooked. There is a marked individual and racial predisposition to the condition. If a person predisposed to this condition receive a wound—which may be very slight, even a prick or scratch being sufficient—the



— 60 μ .

FIG. 12.

Keloid. This consists of dense fibrous tissue in which the fibre bundles have undergone hyaline change, becoming thick and homogeneous in appearance.

resulting scar, instead of contracting, becomes prominent and permanently enlarged. The overgrowth may be so great as to form large pendulous masses. Microscopically the condition is seen to be due to the growth of masses of dense fibrous tissue, often showing hyaline change, in the subcutaneous tissue.

2. *Fibromata of nerves.*—While the typical fibromata are usually single or few in number, there is a condition known as v. Recklinghausen's disease or *molluscum*

fibrosum, in which there is a general fibromatosis. There may be only two or three tumours, or they may be counted in thousands. They occur on the peripheral, spinal, and sympathetic nerves, and in the skin, and are also sometimes found on the cranial nerves and in the central nervous system. The cutaneous tumours have been found to arise in connection with the cutaneous nerves. Structurally these tumours are, for the most part, soft fibromata. They are not encapsulated, but shade off gradually into the fibrous tissue of the nerves or skin. Sometimes some of the tumours may be myxomata, and occasionally one or more may become sarcomatous. The nerve bundles run through the tumours and are often flattened out, the fibres being separated by the overgrowth of fibrous tissue. The cutaneous tumours sometimes form huge pendulous masses. These tumours are often called false neuromata or neurofibromata. Associated with the tumours there is an abnormal pigmentation of the skin.

3. *Fibromata of glands*.—In the medulla of the kidney are sometimes found small fibromata. They do not usually exceed the size of a pea, and show little signs of active growth. In the mammary gland typical fibromata are occasionally found. More common are tumours which are adenomata with an excessive amount of fibrous tissue.

4. *Progressive fibrosis, or diffuse fibroma*.—Associated with the multiple fibromata of nerves there is often a general diffuse fibrosis of the nerve trunks, and this condition may occur independently of the tumours. The overgrowth of the fibrous tissue may cause lengthening of the nerves, which are thereby rendered tortuous—a condition known as “plexiform neurofibroma.” This condition occurring in the nerves of the tongue may give rise to one form of macroglossia. In the mammary gland there may be a diffuse progressive fibrosis involving the fibrous tissue around the acini and ducts. The same process may occur in other situations.

Lipoma.

A lipoma is a tumour composed of fatty tissue. They are rounded soft elastic tumours, often lobulated. They are usually encapsulated and can be shelled out from their sheath readily. Macroscopically, microscopically and chemically they resemble normal fatty tissue. The fat cells vary in size but are usually somewhat larger than normal fat cells. Ordinarily each cell contains a single

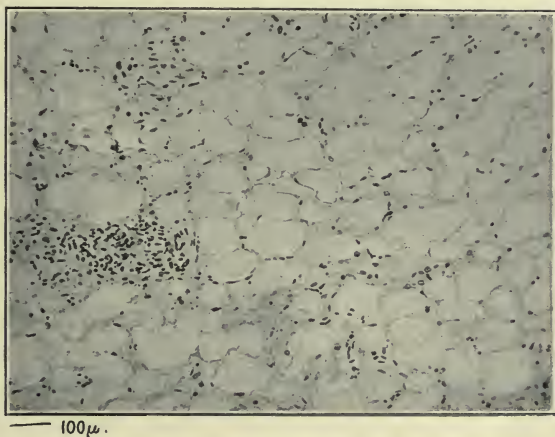


FIG. 13.

Lipoma. Kidney. This shows ordinary fat tissue. At the left is a group of small round cells surrounding a blood vessel.

large fat globule, but occasionally there may be several globules in a single cell. Here and there may be seen areas of polygonal cells, some of which are free from fat, while others contain varying quantities. These are areas in which growth is taking place. The tumour is more or less divided up into larger and smaller areas by fibrous tissue septa, in which run the larger blood vessels. The blood vessels are numerous, and may be dilated. Each of the smaller areas (lobules) of the tumour has its own afferent and efferent vessels, as is the case in normal fat.

Lipomata occur especially in the subcutaneous tissue, frequently about the shoulders, neck, and back. They also occur in the retroperitoneal connective tissue, less commonly in the submucous and subserous coats of the alimentary canal and in the synovial membranes of joints. They rarely occur in glandular organs such as the kidney and in the uterus. They have been found in the brain, eyelids, and other situations in which no fat is normally present. Lipomata are usually single, but may be multiple. They may be of any size, some having been recorded as being fifty or sixty pounds in weight.

Progressive adiposis.—Corresponding to the condition of diffuse progressive fibrosis, we have a condition of diffuse progressive adiposis or diffuse lipoma. In this condition there are more or less localised lipomatous masses which shade off gradually into the surrounding fatty tissue. These masses are often multiple, and are sometimes associated with intense neuralgic pains (*adiposis dolorosa*).

Chondroma.

A chondroma is a tumour composed of cartilage. They form hard elastic tumours, round in shape. When of large size they are distinctly encapsulated. When situated under the skin they, by their growth and unyielding character, so stretch the skin and interfere with its nutrition that ulceration may occur. On section the tumour is easily recognised as containing cartilage. The larger tumours are seen to be divided into numerous lobules by fibrous tissue septa. Degenerated and mucoid areas are common.

Microscopically the tumours are seen to be composed of typical cartilage, usually hyaline, but occasionally fibrous or reticulate. The nodules of cartilage are surrounded by fibrous tissue which carries the blood vessels and acts as a perichondrium. No blood vessels enter the cartilaginous masses themselves. Occasionally the in-

vesting layer of fibrous tissue is absent. The chondrocytes contain glycogen and fat globules.

Chondromata may arise in connection with pre-existing cartilage as in the larynx, trachea, bronchi and intervertebral discs. In these positions they may be localised outgrowths of the pre-existing cartilages or they may have a more independent existence showing no

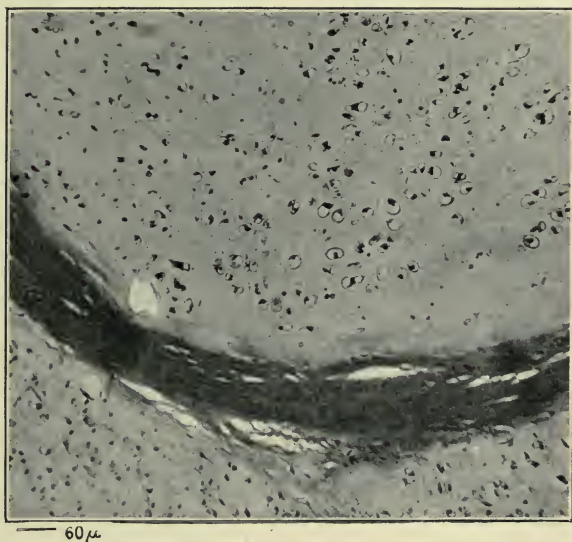


FIG. 14.

Chondroma. This specimen shows masses of typical hyaline cartilage separated by fibrous tissue septa. The chondrocytes are somewhat shrunken. Contrast with fig. 49.

direct - connection with the normal cartilage. More frequently they arise in connection with the bones. Here they are frequently multiple, affecting especially the fingers, but they may arise from any of the long bones. The pelvis is a comparatively frequent seat of chondromata, which may attain a large size. In the bones the chondromata may arise from the surface or from the interior of the bone, especially from the diaphysis towards

the epiphysial end. Apart from cartilage and bone, chondromata may arise in the parotid, submaxillary gland, testis or mammary gland, and occasionally in other situations. In these organs, however, the pure chondromata are rare, while mixed tumours containing cartilage are more common.

Occasionally cartilaginous tumours give rise to metastasis. The majority of these are chondrosarcomata, but in very rare cases metastases have been found which appear to have been derived from pure chondromata.

Chordoma.

The chordoma is a tumour composed of notochordal tissue. This tissue resembles cartilage, but the cells are extremely vacuolated and there is little intercellular substance. Chordomata are rare tumours and of little practical importance. They seldom attain any great size. Their usual situation is in the base of the skull, arising from the basisphenoid. They have also been described as arising in the sacrum.

Osteoma.

An osteoma is a tumour composed of bone. There are many conditions in which bony outgrowths occur, and it is not always easy to determine which of them are to be considered true tumours. The bony callus which is formed at the seat of a fracture is obviously not of the nature of a tumour. We can also exclude the osteophytes which occur in the neighbourhood of arthritic joints and the diffuse thickening (hyperostosis) which occurs in the shafts of the long bones.

Opinion is divided as to whether the outgrowths called *exostoses* are to be considered as tumours or not, but they are, at all events, closely allied to the true tumours, and will be considered here. Exostoses may be composed of cancellous or of compact bone. The cancellous or spongy exostosis is more common in the long bones. It is com-

posed of bone resembling ordinary cancellous bone, and may contain bone marrow. It is covered at one or more points with a thin layer of cartilage. These exostoses are of no regular shape, but form irregular masses of bone, usually pedunculated. They affect chiefly the large bones, whereas chondromata chiefly affect the smaller. Exostoses are frequently multiple and symmetrical. Occasionally somewhat similar growths arise in the interior of the bones and are called enostoses. Compact or ivory exostoses occur especially in the flat bones of the skull and in the jaws. They are usually small round outgrowths with a convex smooth surface. They grow from the outer table of the bone, are covered with periosteum, and contain no cartilage. They are extremely hard and more dense than ordinary compact bone and have the appearance of ivory. In both forms of exostoses there is direct continuity between the tumour and the bone from which it springs.

Apart from exostoses we may have osteomata which are true tumours in the strictest sense. They occur in the cavities of the long bones and in the skull, especially in the antrum of Highmore and in the frontal sinuses. These osteomata show no direct continuity with the surrounding bone. They are quite localised and, in their growth, they distend and destroy the bone in which they grow. Like the exostoses they may be cancellous or compact.

Apart from the bones osteomata may be found in the soft parts. They may be found in the limbs near the bones but not attached to them. Rarely they have been found in other situations such as the mammary gland, trachea or lungs.

We occasionally meet with a progressive hypertrophy of one or more bones, the bones enlarging progressively without definite tumour formation (e.g. leontiasis ossea).

Metaplastic ossification.—We sometimes find masses of bone which simulate osteomata, but are more properly

regarded as resulting from metaplastic ossification. As a rule this ossification is preceded by calcification, and this again by an acute or chronic inflammatory process, while in other cases there does not appear to be an antecedent inflammation. Chondrification may also be met with in similar conditions, and sometimes osteoid tissue, i.e. non-calcified bony tissue, is found. These conditions occur in the choroid following chronic choroiditis or acute panophthalmitis, in the pia mater of the brain or spinal



FIG. 15.

Nodule of cartilage from a hydronephrotic kidney. The kidney was much distended by hydronephrosis and several nodules of cartilage were found in the wall of the dilated pelvis. The other kidney, which was healthy, contained no cartilage.

cord associated with leptomeningitis, in the dura mater and occasionally in the brain itself. They are also found in the pleura, pericardium and peritoneum following inflammation of these serous surfaces ; in the endocardium and intima of the aorta associated with atheroma ; in the trachea, bronchi and lungs ; in the adrenals and in hydronephrotic or cystic kidneys ; and in the septum between the corpora cavernosa of the penis. Ossification and, more rarely, chondrification is also found in tumours.

A good example of progressive metaplastic ossification is myositis ossificans (p. 20).

Odontoma.

Strictly speaking, the term odontoma should be applied to tumours in which the characteristic tissue is dentine.



FIG. 16.

Odontoma. From a section obtained by grinding without decalcification. The main mass of this outgrowth consists of dentine and shows the characteristic tubules. At the lower part is a large piece of enamel in which the prisms can be seen. At the top of the section is a small piece of enamel.

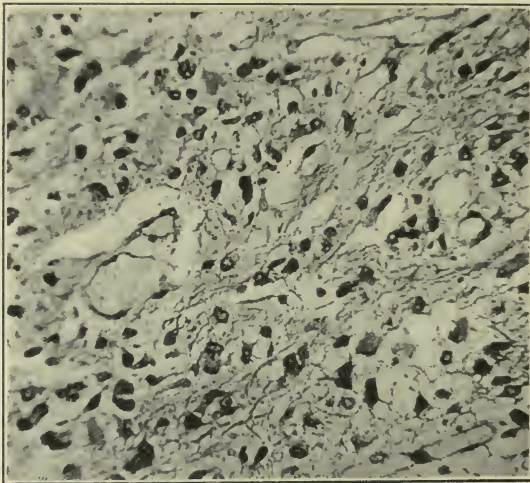
Clinically, however, other tumours of the teeth are called odontomata, such as tumours composed of cementum. Odontomata are rare tumours. They are usually small, but may attain to several ounces in weight. They are found in the upper or the lower jaw, and may grow in the maxillary antrum. They are met with in horses and cattle as well as in man.

Microscopically they consist chiefly of dentine, mixed with which may be varying quantities of enamel or bone (cementum). Sometimes abortive tooth crowns are formed on the surface.

Other tumours of the teeth, clinically called odontomata, are osteomata and fibromata.

Glioma.

A glioma is a tumour composed of neuroglia. They occur in the central nervous system and in the retina



— 20 μ

FIG. 17.

Glioma. Brain. This consists of a feltwork of interlacing fibrils and branched glia cells.

The gliomata of the central nervous system are grey or reddish-grey tumours which, as a rule, are not sharply marked off from the surrounding structures. Owing to the fact that they closely resemble the normal grey matter of the brain or spinal cord, it is often impossible to identify the boundary between the tumour and the normal brain. They may be hard or soft, the hard forms

being more clearly defined than the soft. They do not project above the surface of the brain, but the convolutions lying over them are flattened. In rare cases a glioma may project into one of the ventricles. They usually arise from the grey matter of the cortex or of the central ganglia, rarely being limited to the white matter.

Microscopically a glioma is composed of tissue resembling neuroglia. The cells are usually small with a scanty amount of cytoplasm, and are provided with a large number of extremely delicate processes which interlace with one another, forming a feltwork. Between the cells are numerous fibrils, the relationship of which to the cell processes is not fully determined. In other cases the cells are larger, with a considerable amount of cytoplasm, and the intercellular fibrils are fewer. Retinal gliomata are more cellular than those of the central nervous system. The cells are round or spindle-shaped, and show a perivascular arrangement, the cells at a distance from the vessels having undergone necrosis. The cell processes are indistinct or absent. These tumours are very destructive, causing rupture of the eyeball and destruction of the surrounding tissues. They should strictly be included among the sarcomata (*gliosarcoma*).

In retinal and cerebrospinal gliomata, especially in the former, there are sometimes found spaces lined with a cubical or columnar epithelium which may be ciliated. This epithelium shows no distinct boundary between it and the adjacent tissues, and is homologous with the ependymal epithelium.

(b) *Neuromata.*

Neuroma.

A neuroma is a tumour composed of nerve tissue. Any tumour arising from a nerve is clinically called a neuroma. These are, for the most part, fibromata. A true neuroma contains nerve cells as well as fibres as essential constituents. They are extremely rare tumours, and occur

chiefly in the thoracic or abdominal connective tissue arising from the nerve structures of the sympathetic system. They may arise in the adrenal. Very rarely multiple true neuromata may be found in connection with the peripheral nerves. They may be large tumours, some reaching the size of a child's head. They are hard and

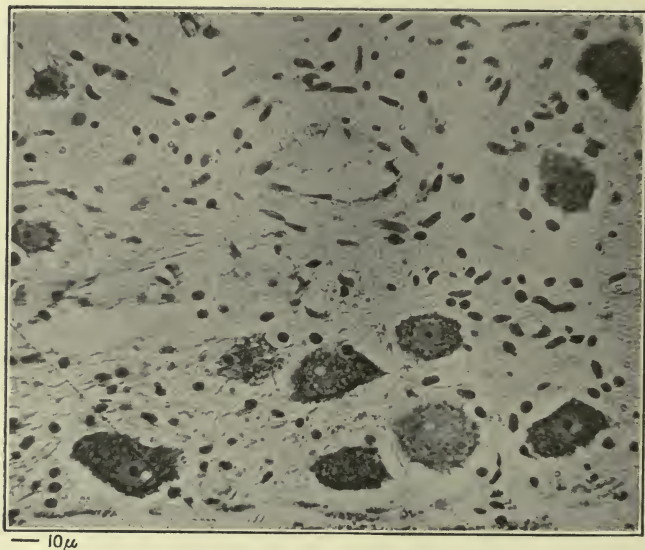


FIG. 18.

Neuroma. Abdominal sympathetic. This tumour was a nodule the size of a marble situated anterior to the inner side of the left adrenal body. Numerous nerve cells can be seen with typical nuclei and nucleoli, and each lies in a nucleated sheath. In each cell there is a small vacuole (? attraction sphere).

have a fibrous appearance. They are composed of nerve cells and convoluted nerve fibres embedded in a stroma of fibrous tissue or neuroglia. The nerve cells may be uni-, bi-, or multi-polar, and are often contained in a nucleated sheath. The fibres may be myelinated or non-myelinated, or both kinds may be present.

(c) Myomata.

Myomata are tumours composed of muscle which may be striated or smooth. Hence we have two sorts of myomata—rhabdomyoma and leiomyoma.

Rhabdomyoma.

The rhabdomyoma or tumour composed of striated muscle is an exceedingly rare tumour. It is more frequent to find striated muscle as a constituent of a mixed tumour than as forming a tumour of itself. The muscle fibres in a rhabdomyoma do not commonly show the typical long multinucleated fibres of normal muscle. They are usually spindle-shaped cells or long irregular fibres with one or more nuclei situated centrally. Often the cells or multinucleated fibres contain a large amount of undifferentiated protoplasm (sarcoplasm), the striated substance or myoplasm occurring as isolated bundles of striated fibrils. These fibrils may be on the surface of the cell or may be distributed irregularly. The fibres show alternating isotropic and anisotropic bands when examined by polarised light. Between the muscle fibres is a fibrous tissue framework. Rhabdomyomata occur in connection with the skeletal muscles and in the heart. They are occasionally found in the oesophagus, uterus, and other situations.

Leiomyoma.

In contrast with the rhabdomyoma the leiomyoma, usually called simply myoma, is a very common tumour. It forms a hard spherical mass which is well encapsulated, and it can be readily shelled out from its sheath. On section it has a white or pink colour, and is seen to be composed of bundles of fibres passing in all directions with a characteristic arrangement in whorls. Microscopically it is composed of typical smooth muscle fibres recognised by the rod-shaped nuclei and staining reactions—e.g. they stain yellow with van Gieson's stain. The muscle fibres

are embedded in a more or less abundant fibrous stroma. Occasionally a myoma contains epithelial tubes and is then called "adenomyoma" (see p. 83). The blood vessels are usually few in number, but sometimes they are numerous and dilated.

Leiomyomata are most frequent in the uterus, especially

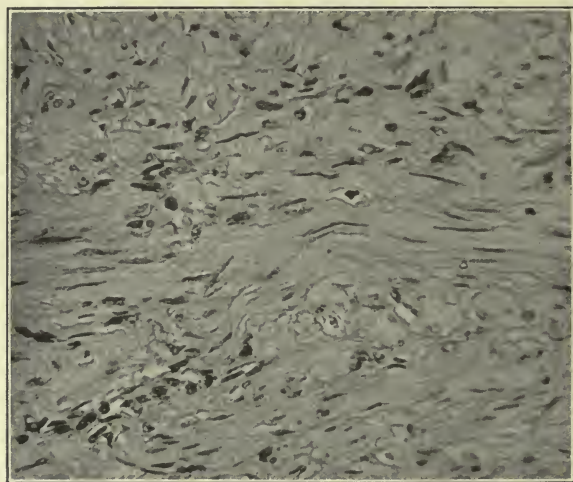


FIG. 19.

Myoma. Uterus. This is composed of unstriped muscle cells between which is a scanty amount of wavy fibrous tissue. The muscle cells are cut in various directions. In the strand passing across the section about the middle they are cut longitudinally and the nuclei appear as elongated rods. Above and below fibres are seen cut transversely or obliquely, the nuclei appearing round or oval.

in the body, and in this situation they are commonly known as uterine fibroids. They are frequently multiple, and may be of any size. Apart from the uterus they are found in the broad ligaments, alimentary canal, skin, prostate, etc.

Myomata, especially in the uterus, are very prone to secondary changes. In some cases the blood vessels of the

tumour are much dilated (angeiectatic myoma). Fatty degeneration is common and is often associated with interstitial extravasation of blood and thrombosis of the blood vessels (red degeneration). The central part of a myoma may degenerate and liquefy so that a cavity results containing fluid (cystic degeneration). Hyaline degeneration may affect the muscle fibres or the fibrous tissue, and calcium salts may be deposited in this degenerated tissue, either on the surface of the tumour or throughout the whole mass. In the latter case the myoma is converted into a solid mass of calcium salts. In a uterus with multiple myomata the separate tumours may show different secondary changes at the same time.

We sometimes find a progressive hypertrophy of the muscular tissue of an organ corresponding to the condition of progressive fibrosis. Such a condition is found in the prostate, uterus and pylorus.

(d) *Lymphomata.*

Although lymphadenoid tissue and bone marrow are widely distributed throughout the body, histiomata composed of these tissues are exceedingly rare and, owing to the nature of the tissue, it is difficult to differentiate them from the corresponding cytomata. Moreover, both the tissues are liable to other progressive changes which are not strictly tumours. Hence has arisen a great confusion regarding the various conditions and the terms used in describing them.

Lymphadenoid tissue and bone marrow belong to the same group of tissues, the function of both being the production of wandering cells (aletocytes) which are discharged, in the one case into the lymph and in the other into the blood. The spleen pulp, again, is a similar type of tissue but with a different function, namely, the function of destroying erythrocytes. For the sake of simplicity it will be advisable to consider the progressive changes to which lymphadenoid tissue is liable. The

results can be applied *mutatis mutandis* to the bone marrow.

Lymphadenoma or Lymphoma.

There is great confusion in the literature as to the various tumours and tumour-like processes which occur in connection with lymphadenoid tissue. This is largely due to the peculiar structure of this tissue. To understand these conditions we must understand the nature of lymph glands and similar organs (spleen, bone marrow). A lymph gland may be regarded as a gland, the essential tissue of which is the endothelium. In some of the lower animals lymphadenoid tissue and bone marrow are represented by definite glands opening directly into the blood vessels and derived from them. The cells lining these glands, of the same origin as the endothelial cells of the blood vessels, proliferate, and the cells resulting from this proliferation pass directly into the blood stream as blood corpuscles. The structure of the blood-forming organs in the higher animals is more complicated but essentially the same. They are to be regarded as true glands, the secretion of which consists of living cells in the same way that the secretion of the sex glands consists of germ cells.

A lymph gland, for instance, consists essentially of an intricate system of channels lined by large endothelial cells which are supported by a delicate connective tissue reticulum. The exact relationship between the reticulum and endothelial cells is not certain. In places there are areas called germ centres in which the reticulum is filled with cells which are somewhat larger than lymphocytes and have a greater amount of cytoplasm. These are the mother-cells of the lymphocytes. They show active mitotic proliferation. The daughter-cells resulting from this proliferation assume the characters of lymphocytes and, passing into the lymph paths of the gland, are discharged into the circulation by the efferent lymphatics.

The mother-cells are themselves probably derived from the endothelial cells of the gland.

The progressive processes arising in lymph glands are the following :

1. Progressive hypertrophy of all the constituents of the gland. This is found affecting all the lymphatic structures of the body in the condition known as *lymphatism*. It is also found locally in some cases of enlarged tonsils and adenoids.

2. There is a histioma of lymphadenoid tissue which consists of the mother-cells of lymphocytes supported by reticulum. It thus has the structure of the germ centres of the lymph gland. It is solitary and does not infiltrate the surrounding tissues. It is one of the rarest of all tumours.

3. Progressive hypertrophy of the endothelial and reticular structures. This is the lesion found in *Hodgkin's disease*, a disease which is also known by a variety of names such as lymphadenoma, malignant lymphoma, lymphadenia, pseudoleukaemia, etc. In this condition there is a great increase in the endothelial and reticular structures with a diminution in the lymphocytes and their mother-cells. Numerous multinucleated cells are found derived from the endothelial cells, and there are often considerable numbers of eosinophile cells. The lymph channels of the gland are occluded by the overgrowth of the endothelial and reticular elements and in cases of long standing the glands may become almost completely fibrous. The diminution in the germ centres may be due to the increased amount of endothelium and reticulum, or it may be due to the fact that the germ centres become exhausted, no new mother cells being produced from the endothelial cells. In Hodgkin's disease a whole group of glands is affected simultaneously. The glands enlarge but remain distinct, although in later stages they may become matted together by adhesions. Other groups of glands subsequently become enlarged and deposits of

lymphoid tissue resembling that of the glands may appear in the viscera (lungs, liver, kidney, etc.).

4. Progressive hyperergasia. This shows itself by the excessive production of lymphocytes which, as we have seen, are to be regarded as the secretion of the gland. It is the condition found in *lymphatic leucocythaemia*. As the result of the hyperergasia the glands enlarge. They

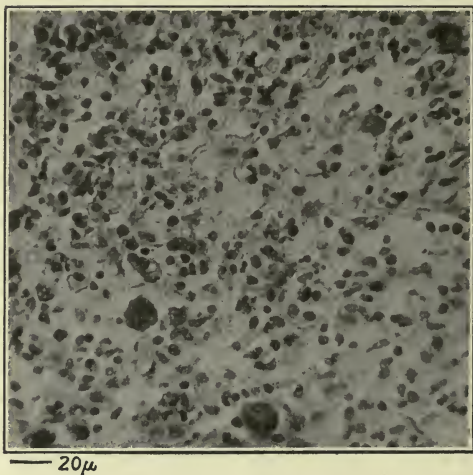


FIG. 20.

Lymphatic gland from a case of Hodgkin's disease. This section shows that the gland is fibrosed by a great overgrowth of the reticulum. The lymphoid cells have almost disappeared, only a few being left in the meshes of the fibrous network. Several multinucleated cells are shown.

remain separate and distinct. The structure of the glands is unaltered, but the germ centres are larger and the lymph paths are crowded with lymphocytes.

5. Lymphocytoma or lymphosarcoma. This is a cytoma composed of cells resembling the mother-cells of the lymphocytes, mingled with which are a varying number of typical lymphocytes. Multinucleated cells may also be present. The cells are supported by a reticulum which

is less perfectly formed than in the normal gland. In this condition we have an increased proliferation of the mother-cells with a diminished transformation of the daughter-cells into lymphocytes. This tumour is considered more fully below (p. 113).

6. Other tumours not composed of lymphadenoid tissue may arise in the glands, e.g. spindle-celled sarcoma, large round-celled sarcoma, etc.

Myeloma.

The progressive changes to which the bone marrow is subject have a close resemblance to the changes described in connection with the lymph glands. Here the wandering cells (aleucocytes) are discharged into the blood stream and include leucocytes and erythrocytes. The changes in the bone marrow may be associated with corresponding changes in the lymph glands or may be independent of them. Progressive hyperergasia of the leucocyte-forming portion of the bone marrow is found in spleno-medullary leucocythaemia, and cases resembling Hodgkin's disease in which the bone marrow was affected have been described.

The myeloma is a rare tumour of bone marrow. It is usually multiple and occurs especially in the ribs and vertebrae. The growth of the tumours may give rise to fractures. The tumour is composed of tissue resembling bone marrow. Usually one type of marrow cell predominates. The condition is associated with the excretion of a peculiar form of protein (Bence Jones protein) in the urine.

(e) *Epithelial and Endothelial Histiomata.*

Histiomata in which the characteristic elements are epithelium or endothelium are structurally similar. The epithelium or endothelium either covers the surface of villus-like processes or forms tubes embedded in connective tissue.

Epithelial Histiomata.

Epithelium being an avascular tissue is dependent for its nutrition on the vascular connective tissue upon which it lies. Hence we cannot have any considerable overgrowth of epithelium without a corresponding overgrowth

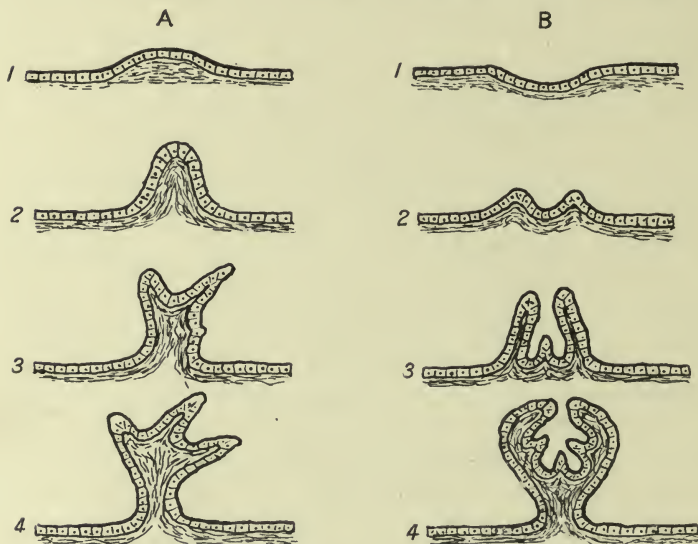


FIG. 21.

Diagram illustrating the formation of papilloma and adenoma. If an area of surface epithelium commence to proliferate and thereby be increased in extent it must become either evaginated as in A1 or invaginated as in B1. In the former case the evaginated area will carry with it the subjacent fibrous tissue to which it is attached, as in A2, thus forming a simple papilloma. This, by a repetition of the same process, may become branched, as in A3, A4. In the case of the invagination the resistance of the subjacent tissues tends to prevent the downgrowth of the proliferating area, so that the edges of the invaginated area rise, as in B2. By a continuance of the same process the tube formed by the invagination may become branched, and the whole area may become pedunculated, as in B3, B4.

of connective tissue. It follows that an epithelial tumour cannot consist of epithelium alone, but always contains more or less connective tissue which forms what is known as the "stroma."

If we suppose proliferation to start in a limited area

of an epithelial surface one of two things must happen—either the proliferating area is evaginated, forming a protuberance projecting above the surrounding surface, or it is invaginated into the subjacent tissues. In the former case the evaginated area will carry with it a central core of connective tissue so that the resulting tumour will be covered on its surface by the proliferating epithelium. In the latter case the epithelium will take the form of tubes embedded in the connective tissue stroma.



— 120 μ .

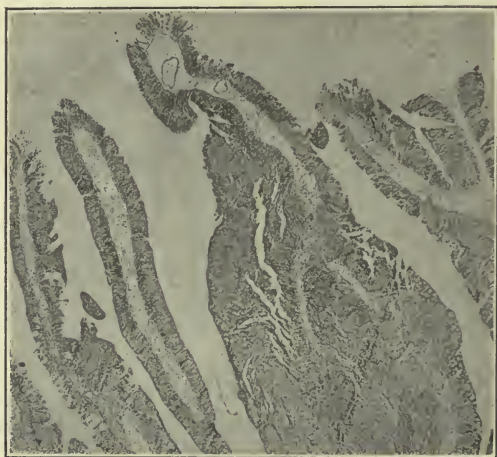
FIG. 22.

Papilloma. Pelvis of kidney. The tumour is an out-growth consisting of a central core of fibrous tissue covered by a many-layered transitional epithelium.

There are thus two types of epithelial histiomata—the *papilloma*, in which the epithelium forms the outer covering of the tumour, and the *adenoma*, in which the epithelium is in the form of tubes or spaces lying in a connective tissue stroma. Both forms may coexist in a single tumour—the *adenopapilloma*.

A papilloma is thus composed of a central core of fibrous tissue covered on the surface by epithelium. The tumour

may be simple or may show branching to any extent. It may be sessile or pedunculated, and may arise from a limited area or be diffuse. An adenoma, on the other hand, is a tumour composed of epithelial tubes lying in a connective tissue stroma. The epithelium and stroma both fairly closely resemble the corresponding elements of the organ in which the tumour arises. The papillomata and adenomata may be considered together.



— 120 μ

FIG. 23.

Papilloma of the bladder. This is composed of long delicate villi, covered by transitional epithelium. Compare with fig. 24.

Squamous-celled papilloma and adenoma.—In the skin we meet with papillomata in the form of *warts*. These may be single or multiple, and may be quite small or may involve a large area of skin. The epithelium covering them resembles epidermis, but it is thicker than normal and the horny cells are more coherent. Sometimes the horny cells cohere to such an extent that they are not thrown off but accumulate, forming a projecting horny mass known as a cutaneous horn.

In mucous membranes covered by squamous epithelium we meet with similar tumours. These are usually softer than the cutaneous papillomata owing to the absence of keratinisation, but sometimes keratinisation does occur. Such papillomata are found in the mouth and larynx. The venereal warts found on the glans penis and vulva have the structure of papillomata, but differ from most papillomata in being highly infective and in being readily cured by remedial measures.



FIG. 24.

Adenoma of the bladder. This was a smooth, rounded pedunculated tumour. It is composed of cavities lined by transitional epithelium. Allowing for the difference in the epithelium, this tumour is exactly comparable with the columnar-celled adenoma of the rectum. See fig. 25.

In the bladder we meet with papillomata consisting of a very delicate stroma covered with transitional epithelium. They are usually pedunculated and show a high degree of branching, forming a mass of long slender villus-like processes. Similar growths may be found in the kidney and ureter.

Occasionally, both in the skin and in the bladder, we meet with squamous- (or transitional-) celled adenomata. These tumours resemble the papillomata very closely in

general characters, but are composed of tubes and spaces lined with squamous or transitional epithelium lying in a connective tissue stroma. They form more or less spherical tumours with a smooth surface. They may be pedunculated. In the skin the epithelium of one of these tumours may become completely keratinised, forming the "subcutaneous horny tumour." Such tumours are sometimes known as "benign epitheliomata."



FIG. 25.

Adenoma of the rectum. This consists of tubes lined with a single layer of columnar epithelium in which are numerous goblet cells. Some of the tubes are branched. Between the tubes is a delicate stroma. Contrast with fig. 56.

Columnar-celled papilloma and adenoma.—In the rectum and in other parts of the alimentary canal we find papillomata, adenomata, and adeno-papillomata. These are essentially the same tumours, differing only in the arrangement of the epithelium.

The papilloma consists of long villous processes, often branched, covered by a layer of typical columnar epithelium. The central core is composed of a delicate reticular connective tissue resembling the normal con-

nective tissue of the intestinal mucous membrane. The adenoma forms a smooth spherical pedunculated tumour composed of epithelial tubes lying in a connective tissue stroma. The tubes resemble crypts of Lieberkuhn except that they are often branched in a complicated manner and there may be communications between neighbouring tubes. The adeno-papilloma or villous tumour is a combination of the above two types, being composed of both villi and tubes.

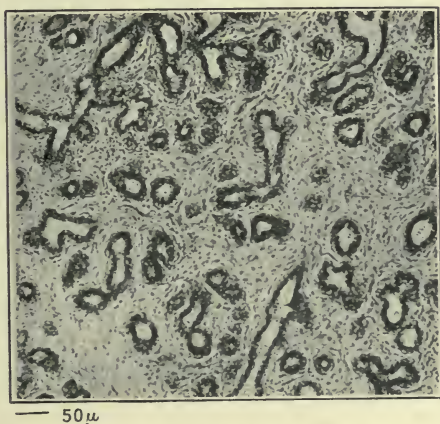


FIG. 26.

Adenoma of the breast. This consists of tubes resembling small mammary ducts. Between the tubes is a fibrous-tissue stroma. There is no lobular arrangement. Contrast with fig. 58.

Columnar-celled adenomata are also found in glandular organs arising from the duct epithelium. They are composed of tubes lined with a uniform layer of epithelium which are not arranged in the manner characteristic of the gland. Thus we do not find acini, and there is no lobular arrangement corresponding to that of the gland. These tumours are common in the breast. They are composed of tubes lined by a double layer of epithelial cells resembling the epithelium of the normal mammary ducts.

The layer next the connective tissue is composed of flattened or cubical cells, while that nearest the lumen consists of columnar cells. In the tubes of an adenoma or in a dilated mammary duct we may find papillomata projecting from the wall into the lumen. Columnar-celled adenomata may also be found in the liver (bile ducts), kidney, sweat glands, and ovary.

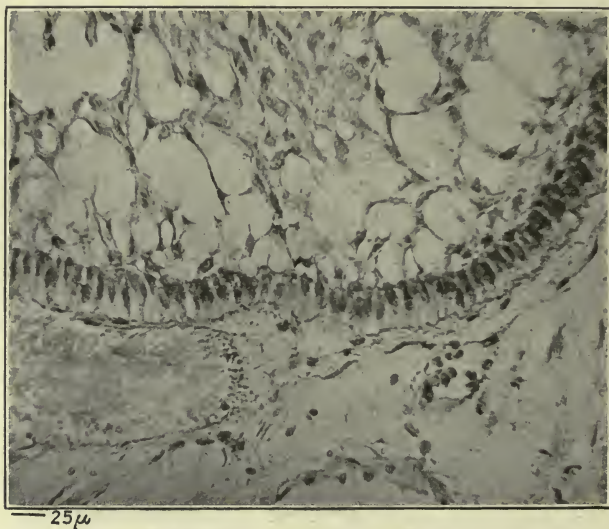
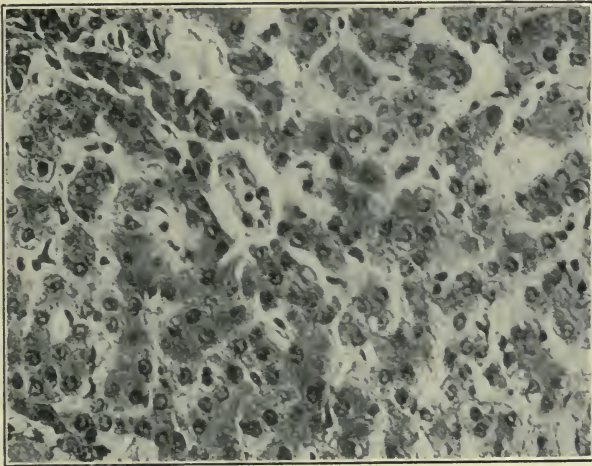


FIG. 27.

Adamantinoma. Lower jaw. The section shows a portion of one of the alveolar spaces. The outer layer of cells which rest on the stroma are tall, columnar cells, which show branches at the free extremities. Above these is a reticular formation composed of branching epithelial cells. This formation corresponds to the pulp of the enamel organ.

A peculiar form of adenoma called *adamantinoma* or "multilocular cystic tumour" is found in the jaws. It arises in connection with the enamel organ of developing teeth and is composed of masses of epithelium, some of which have a central cavity. The outer layer of epithelial cells next the connective tissue are columnar in shape,

but in the more central portions of the epithelial masses the cells have been transformed into stellate cells forming a tissue indistinguishable from mucous tissue in structure and corresponding to the enamel pulp. By a softening and liquefaction of this tissue cavities are formed in the epithelial masses and impart a cystic character to the tumour.



— 25 μ

FIG. 28.

Adenoma of the liver. This consists of columns of cells which are indistinguishable from hepatic cells. The tumour formed a large spherical mass. There were no ducts in any part of the tumour, and there was no lobular arrangement of the cell columns. Contrast with fig. 59.

Spheroidal, or polygonal-celled adenoma.—The spheroidal-celled adenoma or acinous adenoma is characterised by the presence of epithelium resembling the secreting epithelium of the gland in which it originates, but arranged atypically. Thus we do not find ducts, and there is no arrangement into lobules. The stroma and its relation to the epithelium resembles that normally present in the gland. Spheroidal-celled adenomata in those organs in

which the epithelium is not arranged definitely in the form of tubes follow the structure of the organ. Thus a spheroidal-celled adenoma of the liver consists of cells resembling hepatic cells and, like them, arranged in columns with a scanty amount of connective tissue. These columns are not, however, arranged in lobules, and there are no ducts in the tumour. Similarly adenomata of the adrenals show an arrangement of the cells and stroma resembling that of the normal organ. Acinous adenomata of the breast are not so common as the columnar-celled tumours.

The stroma of an adenoma shows much variation in amount. This is especially the case in *mammary adenomata*, in which the fibrous tissue may be present in great excess. In these tumours that part of the stroma which is nearest the epithelial tubes is arranged with the fibres parallel to the wall of the tube, and is usually looser and less dense than the rest of the stroma. It is sometimes difficult, in mammary adenomata, to decide whether the epithelial tubes are a new formation or whether they are the original gland tubes lengthened and distorted by the overgrowth of the fibrous tissue. In the former case the tumour would be an adenoma, in the latter a fibroma or progressive fibrosis. Hence such a tumour is usually called a *fibro-adenoma*, or "adeno-fibroma." Some of these tumours (adenomata) are definitely encapsulated, others are not sharply limited, and may involve a large part of the organ or even the whole (Brodie's disease). These diffuse forms must be regarded as cases of progressive fibrosis, a diffuse overgrowth of the fibrous tissue producing distortion of the original acini and ducts. In many cases the growing fibrous tissue projects into the tubes, invaginating the epithelium before it (intra-canalicular fibroma). In other cases the overgrowth of fibrous tissue may be limited to the regions immediately surrounding the tubes (pericanalicular fibroma). The

fibrous tissue in the intracanalicular forms is of a loose texture consisting of a network of branched cells with few intercellular fibres. Sometimes it has the characters of mucous tissue, while in other cases it may become sarcomatous.

In the uterus and prostate an adenoma may have a stroma containing muscular tissue (*adenomyoma*). This is accounted for by the fact that in the prostate the

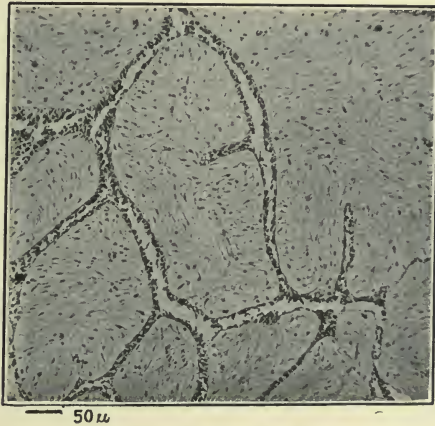


FIG. 29.

Cystic adenoma of the breast (intracystic fibro-adenoma). The epithelial spaces have been almost obliterated by the growth of the surrounding fibrous tissue, which forms masses invaginating the epithelial lining and bring the walls of the spaces into contact.

stroma is largely muscular and in the uterus the uterine glands are normally embedded in the muscular wall to some extent. Hence an adenoma growing from these tubes would naturally have a muscular stroma. Similar tumours may originate in the Fallopian tube or in the broad ligament, where they arise from vestiges of the Wolffian body. The amount of epithelium in these adenomyomata varies. In some cases the tubes are numerous, while in others only one or two spaces lined

with epithelium can be detected. Some of these tumours must be regarded as true adenomata, the epithelium and muscle proliferating simultaneously, while others are due to the overgrowth of the muscle surrounding vestiges of the uterine glands or Wolffian duct.

Both spheroidal-celled and columnar-celled adenomata of glands form spherical or ovoidal tumours which are perfectly encapsulated. They can often be readily shelled out of their sheaths.

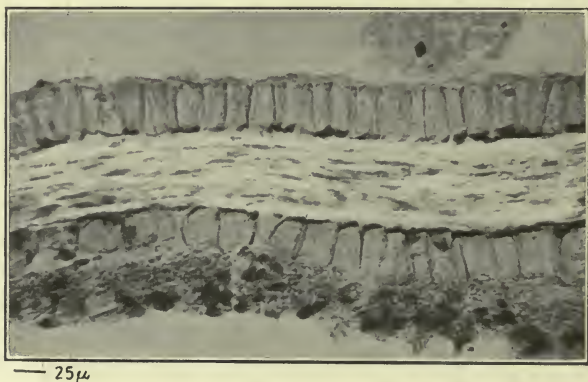


FIG. 30.

Ovarian cyst. This is a section through the septum separating two of the cavities of a proliferating cyst. On each side of the septum is a single layer of tall, columnar, mucin-secreting epithelial cells. The nucleus of each cell is at the basal extremity.

Cystic adenoma.—In some adenomata, especially of the breast and ovary, the tubes and spaces become dilated into cysts. Sometimes, as in the breast, these cysts are empty, the walls being invaginated and brought into contact by the overgrowth of the sub-epithelial fibrous tissue. More frequently, as in the ovary, the cavity of the cyst is filled with fluid secreted by the epithelial cells. Ovarian cysts form the most bulky of all tumours. Before the days of ovariectomy they have been known to weigh as much as the patient in whom they originated.

An *ovarian cystic adenoma* occasionally contains a single cavity, but is more frequently multilocular, consisting of several cavities of different sizes separated by a varying amount of fibrous-tissue stroma. These cavities are lined by a single layer of epithelial cells usually of a typical columnar shape among which are many goblet cells. Sometimes the epithelium is cubical or flattened, and occasionally no lining is to be found, the epithelium having degenerated and desquamated. In the commonest form of ovarian cyst new cavities are continually being formed by budding from pre-existing cavities (proliferating cystadenoma). Other cases are characterised by the growth of intracystic papillomata (papilliferous cystadenoma). Both types of cyst may be found in the same tumour, and one or more of the cavities may have the characters of a teratomatous cyst. In the papilliferous cyst the papillomata may grow to such an extent as to fill the whole cyst and cause its rupture. Occasionally similar papillomata may grow from the germinal epithelium on the surface of the ovary. The fluid in the proliferating cysts is viscid and sometimes almost gelatinous in character. It owes its viscosity to the presence of proteins allied to mucin. In the papilliferous cysts the fluid is more watery. Sometimes, if an ovarian cyst ruptures into the peritoneal cavity the epithelial cells become grafted on to the peritoneal surface and give rise to secondary cysts, each of which has the characters of the primary tumour.

Endothelial Histiomata.

All tumours contain endothelium in the form of blood vessels, but in endothelial histiomata the endothelium is the characteristic constituent, any other tissue present being subsidiary.

Endothelial papilloma.—The endothelial papilloma is a very rare tumour, occurring in the peritoneum, pleura, heart, and aorta. They resemble the epithelial papillo-

mata, the endothelial cells usually taking on epithelial characters and being cubical or even columnar in shape. Pacchionian bodies have the structure of papillomata.

Angeioma.—Corresponding in structure to the adenomata we have a group of tumours called angeiomata which are composed of tubes and spaces lined with endothelium embedded in a connective-tissue stroma. They are formed in connection with blood vessels (*haemangeioma*) or with lymphatic vessels (*lymphangeioma*), but the two forms are anatomically indistinguishable, being recognised only by the nature of the contents of the spaces. These contents are in the one case blood, and in the other lymph, and the connection of the tumours with the blood vessels or lymph channels can be inferred from the fact that the blood or lymph circulates in the tumours.

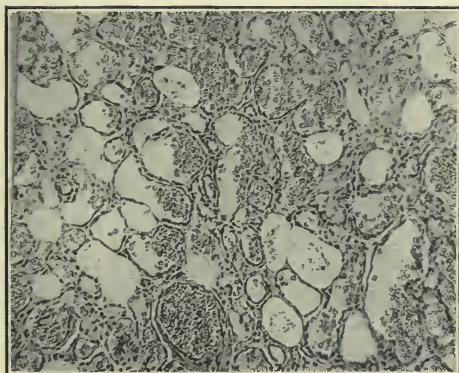
Besides the true angeiomata we also have conditions which are due to an active dilatation of the pre-existing vessels (*angeiectasis*) which may involve a whole organ or a large region. In angeiectasis there is an overgrowth and dilatation of pre-existing capillaries. These increase in diameter and in length, and so become tortuous. Hence a given section will show sections of many more capillaries than the normal, so that it is difficult to say whether or not there is a new formation of capillaries. In some cases the apparent increase in the number of the capillaries may be the conspicuous feature, while in others the increase in diameter may be most evident. This increase in diameter may be so great as to lead to the formation of cysts or vesicles.

Haemangeiectasis occurs especially in the skin, where the condition is known as capillary *naevus*, birth mark, mother's mark, port-wine stain, etc. The lesion may be minute or may involve a large area, as much as half the body being sometimes affected. The affected areas are sometimes sharply limited, and sometimes they shade off gradually into the surrounding skin. Sometimes they are limited to certain nerve areas, and they may be

sharply bounded by the middle line of the body, either in front or behind. Angeiectasis also occurs in the lips and tongue and other situations where the dilatation of the capillaries is the most prominent feature. It may also occur in tumours such as fibromata or myomata.

Lymphangeiectasis occurs in the same situations as haemangeiectasis. In the tongue and lips it is the commonest cause of the conditions known as macroglossia and macrocheilia.

The condition known as *plexiform angioma* or cirroid aneurysm is an angeiectasis affecting arteries, especially those of the scalp. Most of these cases are probably due to dilatation consequent on weakening of the arterial wall and are not of the nature of tumours. Some, however, may be due to an active overgrowth.



— 100μ.

FIG. 31.

Capillary angioma. Subcutaneous tissue. This shows a mass of capillaries separated by a minimum amount of supporting tissue. The capillaries contain blood. Compare fig. 32.

Capillary angioma.—A capillary angioma is a tumour of new-formed capillaries. These capillaries resemble normal capillaries closely, but the endothelium is often more prominent and has epithelial characters, so that the

capillaries resemble gland tubes. The lumen may be almost or quite occluded by this overgrowth of endothelium. Capillary angiomas occur most frequently in the skin and subcutaneous tissue. They are often

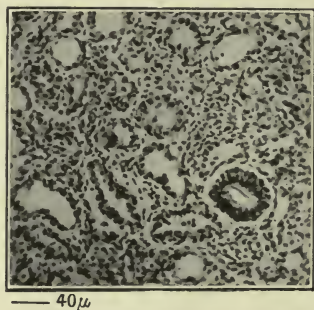
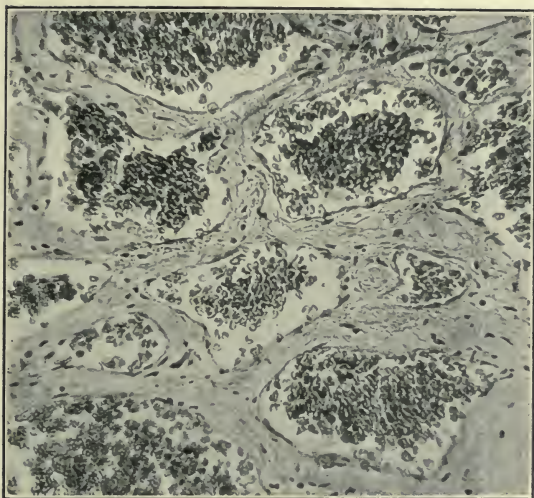


FIG. 32.

Capillary angioma. Parotid. This consists of a mass of capillaries the endothelium of which is unusually prominent and resembles cubical epithelium. Below and to the right is a transverse section of a small duct. Compare with fig. 31.

multiple and sometimes have a definite localisation to the neighbourhood of sweat glands, hair follicles, etc. They are more frequently haemangiomas than lymphangiomas. They also occur in glands.

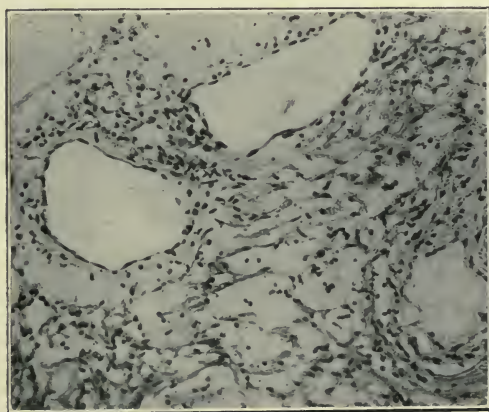
Cavernous angioma.—A cavernous haemangioma consists of large intercommunicating spaces lined with endothelium so that the tumour has somewhat the appearance of erectile tissue such as is found in the corpora cavernosa of the penis. The spaces are irregular in shape and are separated from one another by fibrous-tissue septa. They contain blood which may be fluid or clotted and is occasionally calcified. Cavernous angiomas are commonly seen in the skin, lips, cheeks, mammary gland, and liver. In the liver cavernous angiomas are often multiple and may be of any size, rarely exceeding that of an orange. The spaces of the tumour are supplied with blood by a special vessel derived from the portal vein, and they may also communicate with the capillaries of



— 20 μ

FIG. 33.

Cavernous angioma. Liver. This consists of endothelium-lined spaces separated by thick fibrous-tissue trabeculae. The spaces contain blood. See also fig. 68.



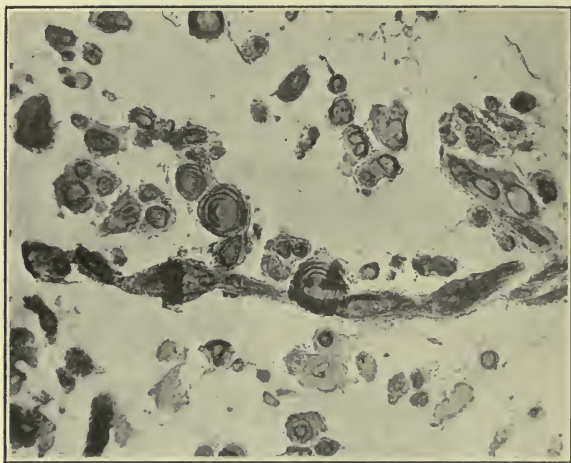
— 40 μ

FIG. 34.

Lymphangioma. Optic nerve sheath. This formed a small spherical tumour on the side of the optic nerve. Three dilated lymph spaces are seen separated by a sponge-like tissue.

the surrounding liver substance. In the fibrous tissue septa there may be found groups of liver cells and bile ducts. As a rule these tumours show little signs of active growth and may be regarded more as malformations than as true tumours. They occasionally, however, grow rapidly and assume formidable characters.

The cavernous lymphangiomata present the same appearances as the haemangiomata, but the spaces are



— 50 μ .

FIG. 35.

Psammoma bodies. These were obtained by submitting a psammoma to artificial digestion. Some of the bodies are spherical and show lamination, while others are long and tubular (calcified capillaries).

filled with lymph instead of blood. They occur as sharply limited tumours in the tongue, lips, skin, etc. They are rare and not so frequent as the lymphangiectases.

Cystic lymphangioma.—Lymphangiomata are frequently cystic and may then form large tumours. They are often called cystic *hygromata* and are most common in the subcutaneous tissue of the neck, axilla, or sacral

region. They may also be found in the mesentery or omentum. They consist of large cavities lined with endothelium and containing a clear or turbid albuminous fluid. Between the cysts is a varying amount of fibrous tissue.

Psammoma.—The term psammoma is applied to certain tumours in which there are numerous calcareous particles which give a gritty sensation to the touch. The commonest form of this type of tumour is found on the inner surface of the dura mater, in the pia mater, or in the choroid plexus of the cerebral ventricles. It is essentially an angioma with a dense fibrous stroma. There is a considerable amount of proliferation of the endothelial cells which form concentrically laminated bodies which become calcified. If such a tumour be submitted to artificial digestion the calcareous particles can be obtained free and are seen to be partly spherical bodies showing distinct lamination, and partly long tubular bodies which are evidently calcified capillaries. Occasionally somewhat similar tumours are found in the peritoneum or tunica vaginalis testis. Calcified particles of similar characters are sometimes found in sarcomata.

CHAPTER VI

CYTOMATA

THE cytomata are tumours in which the characteristic elements are cells which are not arranged so as to form tissues. This description applies only to certain parts of the tumour. In some cytomata formed tissues are found, but they are of secondary origin, being formed from the cells which are the characteristic feature of the tumour. Thus, while in the histiomata the whole tumour is formed of definite tissues, in the cytomata definite tissues may be completely absent and, if present, they never form the whole of the tumour.

In the cells of cytomata *mitotic figures* are often numerous, and a rough indication of the rapidity of growth of the tumour is afforded by the number of mitoses present. In the majority of the cells the mitotic figure resembles that found under normal conditions. The chromosomes are thread-like and divide by longitudinal fission, one-half of each passing to each daughter cell, which thus receives the same number of chromosomes as the parent cell. The normal number of chromosomes in man does not seem to have been accurately determined. Some authors place it at 16, others at 32, and others again at 24. Mitoses in cancer cells are very frequently irregular and this irregularity may show itself in various ways.

1. The number of chromosomes is extremely variable. In some cells there may be very few, while in others they may be innumerable (100 or more).

2. The shape of the chromosomes varies. Instead of

the normal slender threads they may be short and thick, or, again, they may be spherical granules or they may assume the form of rings. In this latter form the chromosomes resemble those found in the heterotypical mitosis which is characteristic of the maturation divisions of the germ cells in which the chromosomes assume the form of rings or tetrads and are reduced to one-half the somatic number. In some of these cases the ring shape is apparent only, being due to two V-shaped chromosomes partially separated from each other.

3. The chromosomes may not take part simultaneously in the various stages of mitosis. Some may be found passing towards the centrosomes, while others are still grouped in the central disc. Hence in the mitotic figure the chromosomes are scattered more irregularly than in normal cell division.

4. As a result of this irregularity in distribution, one or more chromosomes may become isolated and take no part in the formation of the daughter nuclei.

5. The final distribution of the chromosomes may be asymmetrical, one daughter cell receiving less, and the other more, than its share.

6. The division may be multipolar, the cell dividing simultaneously into three or more daughter cells. This is the result of the division of the centrosome into more than two parts. A group of chromosomes passes towards each of the daughter centrosomes.

These multipolar mitoses are common in cytomata, especially in carcinomata. Usually they appear to be tri- or quadri-polar, but occasionally six or eight or even more centrosomes may be seen. In quadripolar mitosis the four centrosomes are usually situated at the angles of a tetrahedron. Hence such a mitosis may appear to be tri-polar if the section includes only three centrosomes, the fourth being in another plane. Similarly a six-polar mitosis may appear to be three- or four-polar. While these irregular mitoses are very frequent in cancer,

they are sometimes met with in other conditions, and they have been induced experimentally in living cells by treating them with poisons such as nicotine and quinine.

Amitosis occurs frequently in cancer. In this form of cell division there is no appearance of separate chromosomes, but the cell divides, either by a septum appearing first in the nucleus and later in the cytoplasm, or by an elongation of the cell which becomes thinned in the middle and eventually separates into two. In amitosis, as in mitosis, the cell or nucleus may divide simultaneously into more than two parts.

As a result of these irregularities in cell division we find various irregularities in the resulting cells. The cells in a cytoma may show great *variation in size*, some being very small, while others may be far larger than any normal cell. This is especially the case in the large spindle-celled sarcoma and in the squamous-celled carcinoma. In columnar-celled carcinoma and in round-celled sarcoma the cells are usually more uniform in size. Another kind of cell frequently found is the multinucleated giant cell which results from mitotic or amitotic division of the nucleus without a subsequent division of the cytoplasm. These giant cells may be found in any form of sarcoma or carcinoma.

Another feature of cancer cells is the frequent presence in them of *cell-inclusions*. They are of various kinds.

1. Leucocytes may be found in the cytoplasm. They usually lie in vacuoles, and may show various stages of degeneration. Their inclusion is to be attributed to an act of phagocytosis on the part of the cancer cell.

2. One tumour cell may contain within it a second tumour cell, and this may contain a third. These included cells show no signs of degeneration, but appear perfectly normal and may be seen to be undergoing mitosis. The outer cell becomes much distended, the cytoplasm being reduced to a thin ring except in the part in which the nucleus is situated. In some cases the inner and outer cells

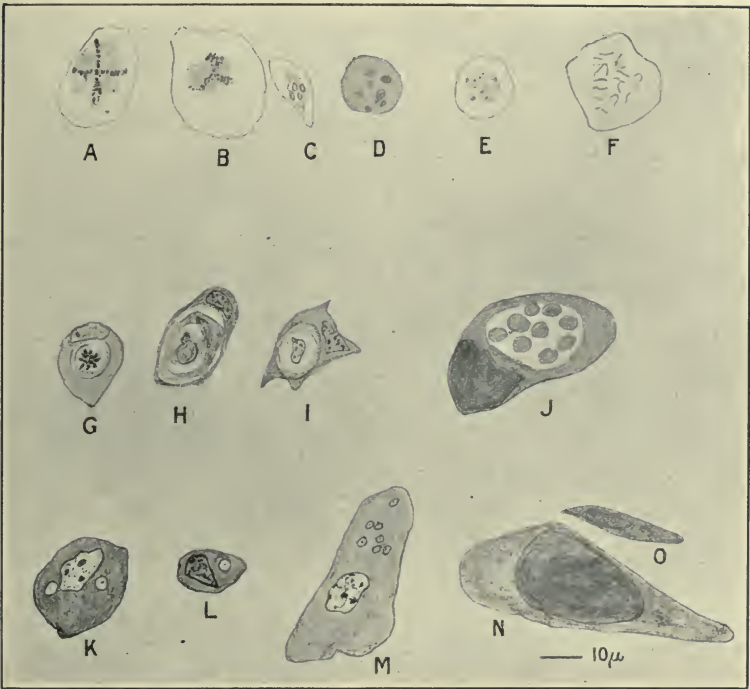


FIG. 36.

Cancer cells. A, Quadripolar mitosis. The chromosomes are arranged in the form of a cross and four centrosomes can be seen between the limbs of the cross. B, Tripolar mitosis. C, Mitosis with ring-shaped chromosomes. D, Karyorrhexis. The nucleus has broken up into several chromatin particles. E, Mitosis. The chromosomes are small and granular and are arranged somewhat irregularly. F, an early stage of mitosis, showing the individual chromosomes scattered through the cell. G, included cell undergoing mitosis while within another cell. H, included cells. The outer cell contains within it a second cell and this, again, contains a third. I, included cell. The cavity in which the included cell lies has a ragged outline. J, a large cell containing several spherical inclusions lying free in a vacuole. K, a cell containing two "bird's-eye" bodies. Each body shows a central spot. L, a cell containing a single "bird's-eye" body. M, a cell containing 7 "bird's-eye" bodies. N, O, two cells from a sarcoma showing the great difference in size. A, C, F, G, L from a carcinoma of the palate. B, D, E, H, I, J, K, M from a carcinoma of the liver. N, O, from a sarcoma of the leg. (Drawing.)

are connected by strands of protoplasm. This suggests that these included cells are the result of an irregular form of cell division, one of the daughter cells being formed within the other (endogenous cell formation). More frequently the inner cell lies in a vacuole, the inner surface

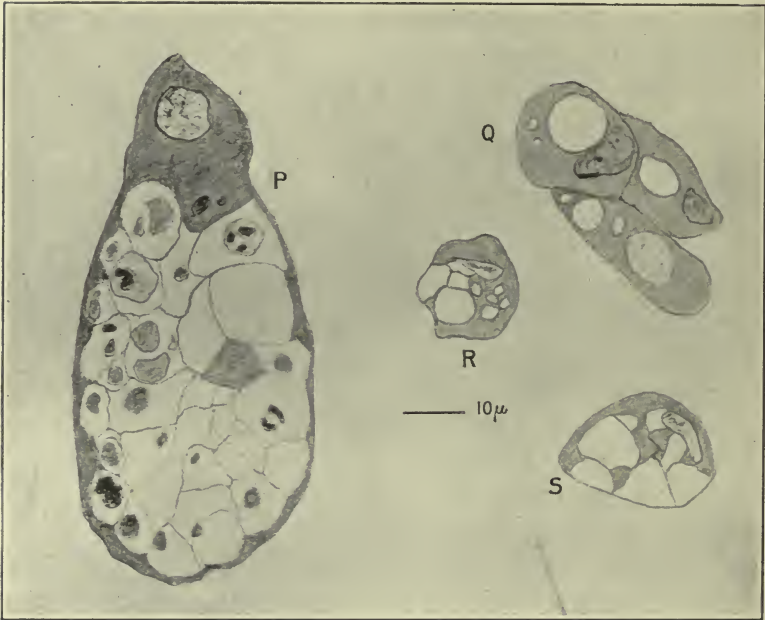


FIG. 37.

Cancer cells. P, a very large cell from a carcinoma of the liver. It contains a large number of various kinds of cell-inclusions. Some are nucleated, others non-nucleated, and others are free chromatin particles. Two are leucocytes. Q, R, S, vacuolated cells from a carcinoma of the pleura. (Drawing.)

of which is ragged and radially striated as if the inner cell has separated from the outer. These cells may be proved to be included by the study of serial sections. Somewhat similar appearances are given by a cell which has partially invaginated another cell.

3. Frequently in cancer cells there are found non-nucleated masses of protoplasm of circular outline when seen in section. Some of these lie in a vacuole while others appear to be continuous with the cytoplasm of the cell. Some of these appearances are due to the section having passed through the cytoplasm, but not through the nucleus, of an included cell.

4. *Plimmer's bodies* or "bird's-eye bodies" are small spherical bodies containing a central granule. They are often radially striated. These are probably of archoplasmic origin, i.e. derived from the archoplasm which forms the centrosome and the achromatic fibres of mitotic cell-division. They are analogous to the archoplasmic vesicles which are found normally in the spermatogonia of the testis. Centrosomes may be found in cancer cells even in the resting condition. They appear as a pair of minute granules.

5. In mitosis the nucleoli usually disappear. Sometimes, however, they remain and, in that case, they may form extra-nuclear inclusions in the daughter cells.

6. In mitosis, especially if irregular, some of the chromatin may be isolated and remain as an extra-nuclear chromatin granule. Similarly the nuclear chromatin of included leucocytes which have degenerated may remain in the cytoplasm of the cancer cell.

7. The nucleus of the cell may break up into several chromatin fragments (karyorrhexis).

8. Lipoids, especially in the form of fluid crystalline globules, may be found in the cytoplasm. Fat globules may also be found, either as degeneration products, or as characteristic features of the tumour (e.g. in adrenal tumours).

9. Globules and clumps of mucin, colloid, hyaline substance or keratin may be found as spherical or irregular cell-inclusions. Some of these may also be found between the cells. The hyaline globules form the bodies known as "fuchsine bodies."

10. Glycogen is often found in cancer cells in the form of clumps or in a more diffuse condition.

11. Watery fluid may be found in the cells. Such cells in prepared sections appear to contain one or more empty vacuoles (hydropic degeneration). These vacuoles may be in the nucleus or in the cytoplasm. They are common in the cells of carcinomata of the pleura and peritoneum.

The interest in these different kinds of cell-inclusions lies in the fact that they indicate abnormal function (e.g. phagocytosis) on the part of the cancer cell: in times past many of them have been taken for parasites.

It must be remembered that in cancer we have cell proliferation going on at a rate which is unknown in any other condition in grown-up animals, and many of the appearances, both as regards the irregularity of mitosis and as regards cell-inclusions, may be the result of this great rapidity of proliferation.

The general features of the cytomata are: (1) they are usually of rapid growth; (2) they are not encapsulated but infiltrate the surrounding tissues, so that no sharp boundary can be seen between the tumour and the surrounding structures; (3) they tend to give rise to metastases, i.e. to secondary tumours at a distance from the primary tumour; (4) they have a disturbing influence on the general health apart from the local effects. Thus the cytomata include those tumours which are classed clinically as *malignant*.

The cytomata are subdivided according to the kind of cell which forms the characteristic feature of the tumour. Thus we have:

Blastocytomata, or tumours characterised by the presence of indifferent cells, i.e. of cells which can give rise both to epithelial and to other types of cells.

Sarcomata (desmocyto~~mata~~), or tumours composed of desmocytes (supporting tissue cells).

Myocytomata, or tumours composed of muscle cells.

Neurocytomata, or tumours composed of nerve cells.

Lymphocytomata, or tumours composed of lymphoid cells.

Carcinomata, or tumours composed of epithelial cells.

It is sometimes difficult to say to which of these groups a given tumour belongs, since cells of different characters often bear a close resemblance to one another. Thus we cannot recognise an indifferent cell as such. We can only recognise a blastocytoma by the fact that in it we find epithelial cells, fibrocytes, myxocytes, chondrocytes, myocytes, etc., and we can determine that these are all derived from the same kind of cell. The difficulty is especially great in regard to endothelial cells. When a tumour arises from endothelial cells these are apt to lose their characteristic features and become indistinguishable from epithelial cells so that an endothelial cytoma is often indistinguishable from a tumour formed of epithelial cells. On the other hand, some parts of an endothelial cytoma may resemble a sarcoma. The same difficulty sometimes occurs in distinguishing between a sarcoma and a carcinoma. A definite conclusion can be arrived at in many cases only by examining several distinct parts of the tumour.

Blastocytomata.

The great majority, if not all, of the malignant tumours of the kidney in infancy belong to this genus. These tumours are often called sarcomata (*adenosarcoma*, *rhabdomyosarcoma*, etc.), but they are distinguished from the sarcomata by the presence in them of epithelial tubes as essential parts of the tumour. They form large soft tumours often some pounds in weight. On section they are lobulated and white or pink in colour. They may contain cysts visible to the naked eye. The remains of the kidney are usually seen stretched out on the surface of the tumour, and are infiltrated to some extent by the growth.

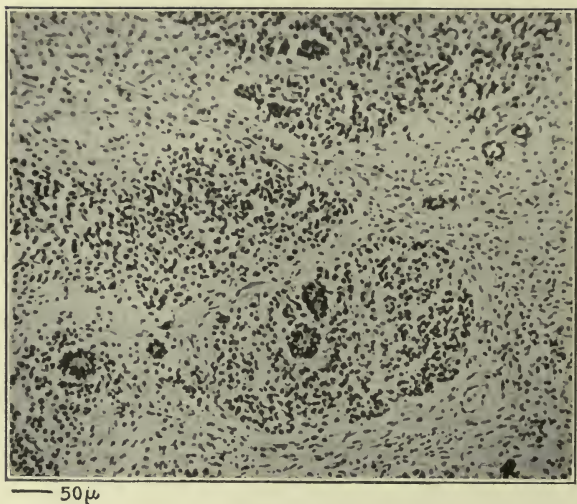


FIG. 38.

Blastocytoma of the kidney. There are several groups of small round cells separated by a spindle-celled cellular tissue. Among the small round cells are several epithelial tubes in various stages of differentiation. See also fig. 39.

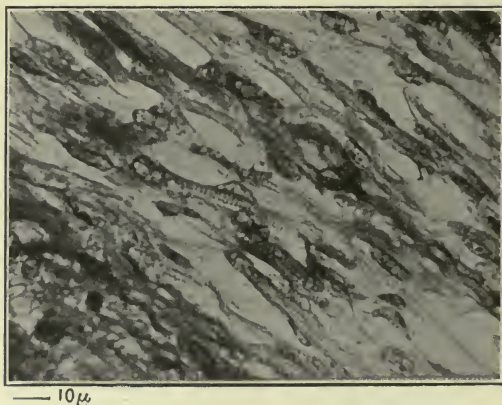


FIG. 39.

Blastocytoma of the kidney. This section shows the striated muscle fibres which are formed in this type of tumour. The fibres are long, cylindrical or spindle-shaped cells with one or more nuclei—usually central in position.

Metastases may be present in the glands, lungs or liver, but are often absent.

Microscopically such a tumour presents different appearances in different parts. One part may have all the characters of a round-celled sarcoma ; in other places rows of spindle cells, or definite fibrous tissue forms a

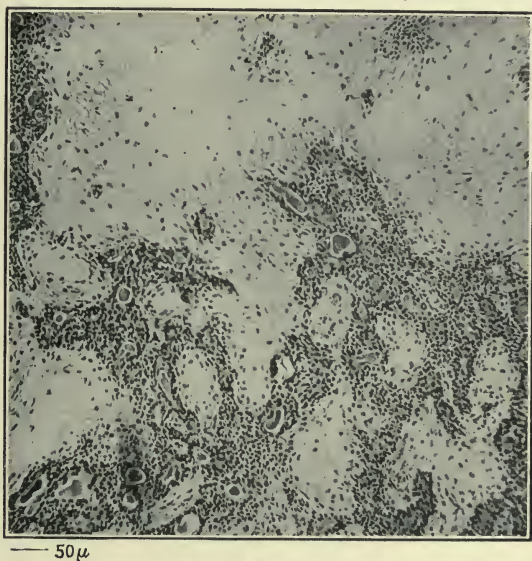


FIG. 40.

Blastocytoma of the parotid. Parotid tumour. In the lower part of the section are seen masses of closely packed cells which in several places form definite tubes with homogeneous contents. These cell masses shade off without a sharp demarcation into the loose mucous tissue seen chiefly in the upper part of the section. See also fig. 41.

network enclosing alveoli which contain masses of round cells embedded in which are small epithelial tubes. In other places, again, the epithelial tubes may predominate so as to give the appearance of an adenoma or carcinoma. Fibrous tissue, mucous tissue, fat, cartilage, bone, smooth and striated muscle may all be present in different parts.

If we examine such a tumour minutely we can determine that these different constituents are not independent of one another, but that all can be traced to the round cells which form the fundamental cells of the tumour. Thus, on the one hand we can find all stages between the round cells and the epithelial cells and, on the other,

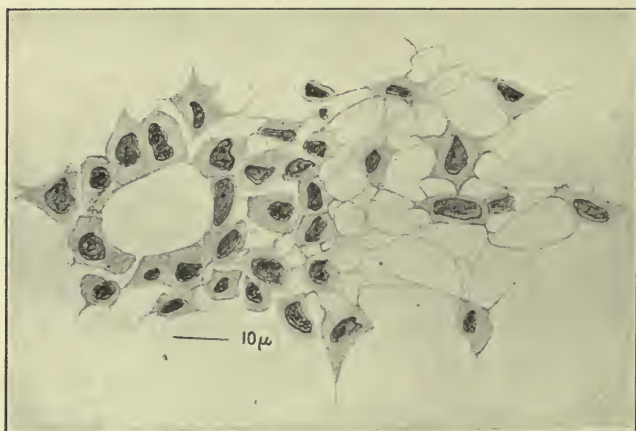


FIG. 41.

Blastocytoma of the parotid. On the left is seen a tube formed of epithelial cells, which show intercellular bridges. On the extreme right is the mucous tissue, composed of cells with long processes, which anastomose and interlace with one another. The section shows the continuity between the epithelium and the mucous tissue. In the epithelium the cells are close together and the intercellular connections are short, while in the mucous tissue the cells are widely separated and the intercellular connections long, the spaces between the cells containing a mucin-containing substance. (Drawing.) See also fig. 40.

between the round cells and the mucous tissue and other forms of supporting tissue which may be present, and so to the muscle cells. Hence the round cells must be regarded as indifferent cells or blastocytes.

Another common seat for these tumours is the parotid gland. The *mixed tumours of the parotid* are composed of epithelial tubes, solid columns of epithelial cells, mucous

tissue, fibrous tissue, cartilage, etc., with groups of cells resembling sarcoma cells. Here, again, we can trace all stages of transition between the epithelial cells and the supporting tissue cells, both apparently being derived from intermediate polygonal cells which are united together by intercellular bridges. By approximation of these cells epithelial cells are formed, the intercellular bridges becoming prickles. On the other hand, by the separation of the cells by the intervention of a mucoid intercellular substance while the intercellular bridges are lengthened to form long processes joining cell to cell, mucous tissue is formed and, by a further transformation of the intercellular substance and an alteration in the characters of the cells we obtain cartilage.

Blastocytomata also occur in the submaxillary gland and other parts of the region of the mouth, in the skin, brain, uterus, testis, sacral region, pharynx, etc.

Sarcomata.

The sarcomata are malignant tumours composed of desmocytes and tissues derived from them only. They are usually rapidly growing tumours, infiltrating the surrounding tissues, though in some cases the edge may appear to be sharply limited. They give rise to metastatic tumours. The outline may be spherical or irregular, according to the situation of the tumour. The surrounding tissues are compressed as well as infiltrated. The consistency of the tumour varies according to its structure and rate of growth. Some are very soft, almost diffuent, while others may be firm or hard. The presence in them of fibrous tissue, cartilage, or bone may be recognised by the naked eye. The colour is also variable according to the amount of blood contained in them. Some are white, while others may be so full of blood as to resemble a blood clot. Some sarcomata are pigmented, showing a brown or black colour.

Microscopically the cells can be seen infiltrating the

surrounding tissues beyond the apparent limits of the tumour. The cells are of various forms, and show a considerable amount of cytoplasm and well-marked nuclei, round or oval in shape, which often stain rather faintly. Mitotic figures are numerous and often irregular. The cells often contain intracellular bodies or inclusions.

The blood vessels are numerous and imperfectly formed, consisting of capillaries and irregular spaces lined by a single layer of endothelial cells which are in contact with the tumour cells. The larger spaces may show a thin fibrous layer beneath the endothelium, but definite arteries and veins are not found except those which pre-existed in the part which is being infiltrated by the tumour. Lymphatics are absent or very scarce. The tumour cells often show a definite arrangement with respect to the vessels being arranged parallel or radially to them.

The intercellular substance in some cases is very slight in amount so as to be recognised with difficulty, while in others it is present in considerable bulk. It may be homogeneous, granular, or fibrillated, or it may show the characters of mucoid tissue, cartilage, etc.

Sarcoma may arise in any part of the body and from any form of connective tissue. In rare cases we find sarcoma arising in all parts of an organ simultaneously without forming a definite tumour. Such cases are called diffuse sarcoma or diffuse sarcosis.

Sarcomata are classified according to the kind of cell, and according to the type of tissue which may be present. Thus we have *pure sarcomata* in which no formed tissues are present and *compound sarcomata* in which there are definite tissues of secondary formation.

<i>Pure sarcomata.</i>	Round celled
	Spindle celled
	Melanotic
	Giant celled

Compound sarcomata. Myxosarcoma
Fibrosarcoma
Chondrosarcoma
Osteosarcoma
Osteoid sarcoma
Gliosarcoma
Chordosarcoma

and combinations of these. Besides these tumours there is the tumour called *angiomasarcoma*, the structure of

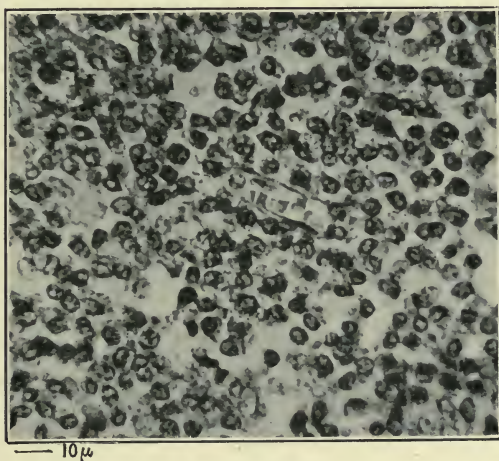


FIG. 42.

Small round-celled sarcoma. Subcutaneous tissue. The cells are very uniform in size—a little larger than lymphocytes—and contain large nuclei. Near the centre is a capillary containing erythrocytes. It consists merely of a tube of endothelium, which rests directly on the tumour cells. Compare with fig. 43.

which it is difficult to interpret. This is apparently of endothelial origin, and will be described with the endothelial cytomata.

Pure Sarcomata.

These consist merely of cells with a slight amount of intercellular substance. The type of cell may be constant

in all parts of the tumour, or it may vary in different parts. We may also have mixed-celled sarcomata in which cells of different types exist side by side.

Round-celled sarcoma.—A round-celled sarcoma consists of little more than a mass of round or polygonal cells with a small amount of intercellular substance. The cells may be small or large. The small round-celled sarcoma is

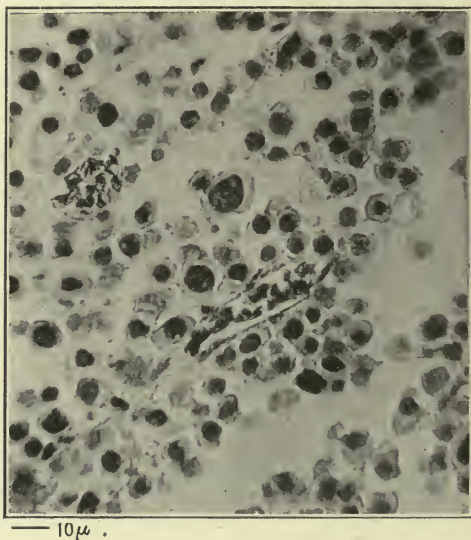


FIG. 43.

Large round-celled sarcoma. Testis. The cells are large and round or polygonal in shape and have large and distinct nuclei. Here and there can be seen traces of a delicate reticular stroma. Near the centre is a capillary. Compare with fig. 42.

the most malignant of all the sarcomata, growing rapidly, infiltrating and giving rise to metastases. The cells are rather larger than lymphocytes, but the nuclei stain less deeply, and there is a larger amount of cytoplasm. The intercellular substance is scanty and is homogeneous or granular. Sometimes it is fibrillated.

The large round-celled sarcoma consists of large cells

which often lie in groups in the meshes of a fibrous stroma. The cells resemble epithelial cells, so that it is sometimes difficult to distinguish this type from a carcinoma. It is probably of endothelial origin.

Round cells are also met with in chondrosarcomata, blastocytomata, and lymphocytomata.

Spindle-celled sarcoma.—The spindle-celled sarcoma is composed of spindle-shaped cells with round or oval nuclei,

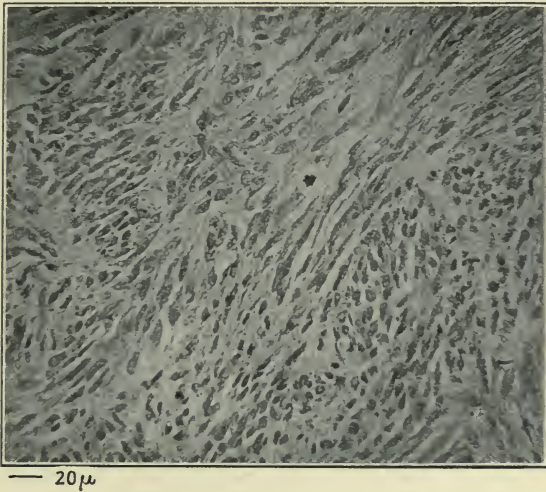


FIG. 44.

Spindle-celled sarcoma. Rectum. The tumour consists of groups of spindle-shaped cells running in various directions. Some of these are cut longitudinally and others transversely. Just above the centre of the illustration is a cell undergoing mitosis. See also fig. 5.

and a delicate fibrillated intercellular substance. The cells are arranged parallel to one another in fasciculi. The size of the cells varies, but it is not possible to subdivide this type of sarcoma into definite varieties. We may have oval cells differing but slightly from the cells of a small round-celled sarcoma, and we may have various sizes of definite spindle-shaped cells. In the larger forms

the cells may take various shapes, either simple spindles with long processes at each end, or the processes may be forked or the whole cell may be irregularly branched. It is not uncommon to find cells with several nuclei. The fibrillated intercellular substance is composed of long delicate fibrils which are interlaced with the processes of the cells. This intercellular substance is often slight in amount and difficult to detect.

Melanotic sarcoma.—A melanotic sarcoma is a sarcoma composed of cells containing melanin. This is a pigment similar to the pigment of the choroid and the skin. It contains no iron, but contains sulphur as well as carbon,

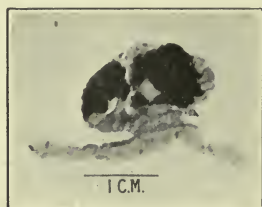


FIG. 45.

Melanotic sarcoma. Skin. This forms a pedunculated tumour, which is deeply pigmented. It arose from a pigmented mole which, for some years had been excoriated by the friction of the clothing.

hydrogen, nitrogen, and oxygen. It is a metabolic product of the cells and is not derived directly from blood pigment. A melanotic sarcoma may be of any shade of brown according to the amount of melanin present. Those with a large amount of pigment appear quite black.

Histologically this tumour is either a spindle-celled or a large round-celled sarcoma, and often tends to show an alveolar structure. The cells are crowded with brown granules of melanin and similar granules may be found between the cells. There are also varying numbers of

unpigmented cells, the proportions between the pigmented and the unpigmented cells varying greatly.

This tumour is extremely malignant, and a small primary tumour may give rise to enormous masses of metastatic growths especially in the liver. In severe cases melanin or a colourless melaninogen may appear

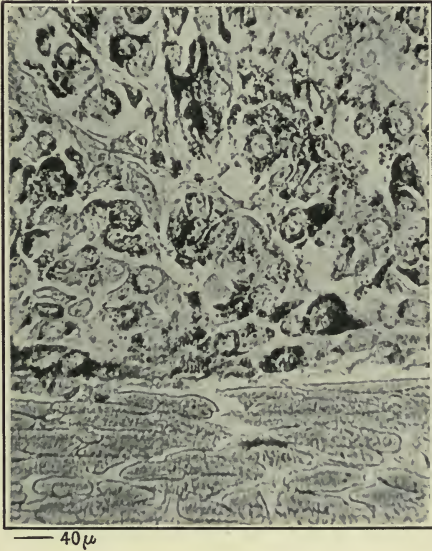


FIG. 46.

Melanotic sarcoma. Skin. From a metastatic tumour in the heart. The section shows the tumour to be composed of large cells, many of which are loaded with granules of pigment. Below are seen the cardiac muscle fibres.

in the urine. The usual seats of origin are the choroid of the eye and the skin, especially in pigmented moles.

Giant-celled sarcoma.—The giant-celled sarcoma is the least malignant of the sarcomata. It is locally destructive, but very rarely gives rise to metastases. The usual situation is the interior of the bones arising from the endosteum, and, from the resemblance of the giant cells

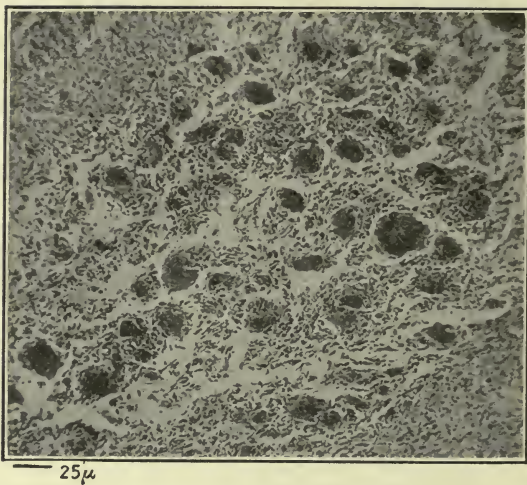


FIG. 47.

Giant-celled sarcoma. There are numbers of multinucleated giant cells between which are smaller round or spindle-shaped cells. See also fig. 48.

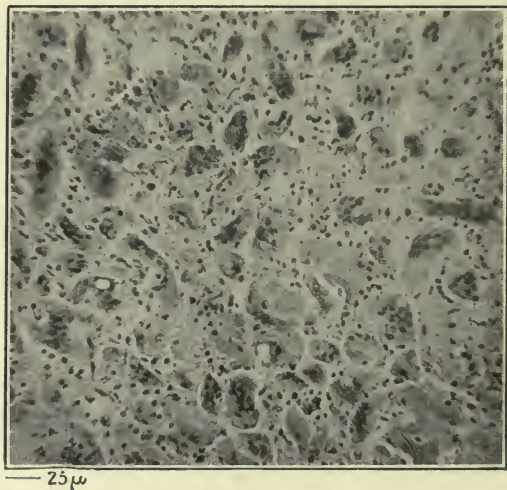


FIG. 48.

Giant-celled sarcoma. From the femur of a drake. Notice the close resemblance to fig. 47. In this case there were metastatic tumours in the liver.

to osteoclasts, it is often called *myeloid sarcoma*. Another common seat is in the gums, where it grows from the periosteum of the alveolar process of the jaw and forms what is known as the *malignant epulis*.

Macroscopically the tumour is deep red in colour or may be mottled with white or yellow areas. It shows a great tendency to break down and undergo necrosis.

Microscopically the characteristic feature is the presence of large multinucleated cells in great numbers. These giant cells contain several nuclei scattered throughout the cell; they resemble osteoclasts and are different from those of bone marrow or of tuberculosis. Similar giant cells may occur in sarcomata in other situations, but it is rare to find a definite giant-celled sarcoma apart from the bones. Besides the giant cells the tumour contains spindle-shaped and branched cells.

Compound Sarcomata.

The compound sarcomata are distinguished by the fact that the cells of the tumour give rise to definite formed tissues. They are, as a rule, less malignant than the pure sarcomata. When they give rise to metastases these have the same characters as the primary tumour. These compound sarcomata may be regarded as sarcomata in which the characteristic cells are the cells corresponding to the definite tissue which is present. Thus the cells of a chondrosarcoma may be regarded as chondrocytes, those of an osteosarcoma as osteocytes, etc., whereas the cells of a pure sarcoma have no such definite characters.

Chondrosarcoma.—This may be taken as the type of a compound sarcoma. In the actively growing part of the tumour the cells are round or polygonal. In places throughout the tumour the cells are separated by the laying down of a cartilaginous matrix, a product of the cells themselves. The cells thus separated assume the characters of ordinary chondrocytes.

Osteosarcoma and *osteoid sarcoma* resemble chondro-

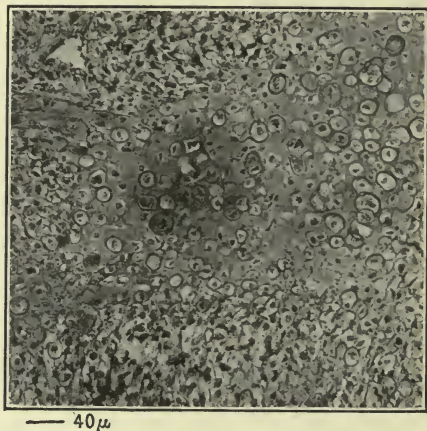


FIG. 49.

Chondrosarcoma. Below and above are seen sarcoma cells. In the middle is a mass of hyaline cartilage formed by the laying down of a cartilaginous matrix between the cells. Contrast with fig. 14.

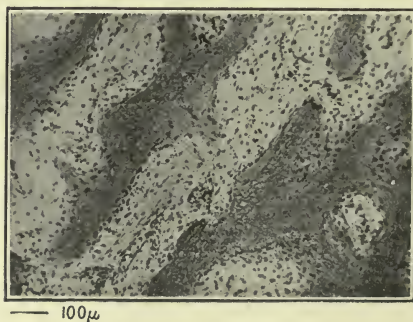


FIG. 50.

Osteoid sarcoma. This is from a metastatic tumour in the lung, the primary being in the femur. The section shows trabeculae of osteoid tissue—i.e. bony tissue which is not calcified. Between the trabeculae are sarcoma cells.

sarcoma except that in osteosarcoma true bone, and in osteoid sarcoma non-calcified bony tissue are formed.

These three compound sarcomata usually arise in connection with bones, but they may occasionally arise in other positions such as the mammary gland.

Other compound sarcomata are *myxosarcoma*, *fibrosarcoma*, *gliosarcoma*, and *chordosarcoma*.

Myocytomata.

Cytomata composed of muscle cells are rare tumours. They closely resemble the sarcomata in general characters, but the proliferating cells are muscle cells, either smooth or striated. Myocytes are found as constituents of mixed tumours (blastocytomata) more commonly than as forming a cytoma of themselves. Leiomyocytomata are sometimes found in the uterus.

Neurocytomata.

Neurocytomata are even rarer than myocytomata, only one or two specimens having been described. They resemble the sarcomata in general characters and give rise to metastases. The cells in their young stage are round in shape, but become branched and resemble nerve cells in the older parts of the tumour.

Lymphocytomata.*

The lymphocytoma is a cytoma in which the characteristic cells resemble the cells of the germ centres of lymphatic glands. Mixed with these, and derived from them, are a varying number of typical lymphocytes. The cells are supported by a delicate reticulum resembling the lymphoid reticulum. There is no intercellular substance, the cells lying in groups in the meshes of the reticulum. The reticulum varies in amount in different parts of the tumour, being absent where the cells are invading the surrounding tissues. Associated with the reticulum are

* These tumours are usually called *lymphosarcomata* in this country, but as the cells are not those of supporting tissues, it is better to use the term lymphocytoma which is used in France and Germany.

large endothelial cells. Multinuclear cells may also be present.

Lymphocytomata arise especially in lymphatic glands and in lymphoid tissue generally (stomach, intestines, tonsils, etc.). They form large tumours invading and destroying surrounding structures, and form metastases in distant parts.

Chloroma.—This is a peculiar tumour having the

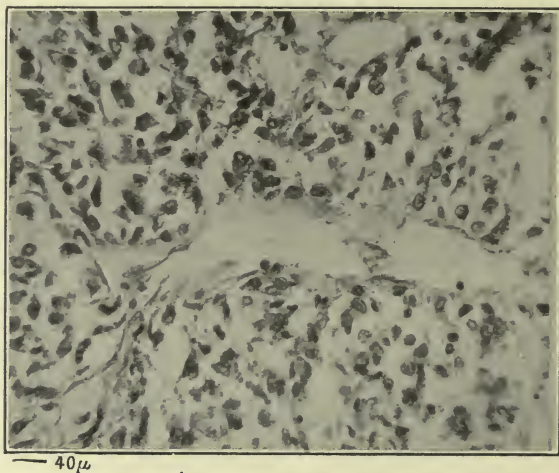


FIG. 51.

Lymphocytoma. Mediastinal glands. This is composed of cells resembling lymphocytes and the mother cells of the germ centres. The cells are supported by a delicate reticular stroma resembling the lymphoid reticulum. In the centre is a large blood vessel.

structure of a lymphocytoma, but showing, when freshly exposed, a bright green or yellow colour which fades quickly on exposure to air. The tumour forms flattened, somewhat diffuse growths on bones. Metastases are found in lymph glands and in internal organs. It is usually associated with a leucocythaemic condition of the blood. The green colour is due to a fat-containing

pigment, the nature of which is not known. The pigment is associated with fluid crystalline globules in and between the cells.

Occasionally we meet with a *myelocytoma*, a tumour in which the characteristic cells are myelocytes.

Carcinomata.

An epithelial cytoma or carcinoma is a tumour characterised by the presence of masses of epithelial cells embedded in connective tissue stroma. In the pure carcinoma, such as is seen in the typical scirrhous of the breast, no arrangement of the cells to form a definite epithelium is found, while in other carcinomata, analogous to the compound sarcomata, definite epithelium is formed by a secondary arrangement of the epithelial cells. These latter forms are called *adenocarcinoma* or *papilocarcinoma*, according as the epithelium forms tubes and spaces or papillary excrescences.

A carcinoma, then, consists of columns and masses of epithelial cells which appear to be contained in spaces bounded by connective tissue. These spaces are called alveoli. They are not closed spaces, but communicate freely with each other, so that, if the epithelial cells are removed, the remaining fibrous tissue stroma has a structure resembling that of a sponge. In microscope sections these spaces are cut across in various directions, giving the appearance of closed areas of different sizes and shapes filled with epithelial cells. The size of the alveoli varies greatly. Sometimes an alveolus will contain only two or three cells, while at other times it will be large enough to be visible to the naked eye. The carcinomata with small alveoli have a relatively large amount of stroma and are hence hard to the touch, and are called hard or scirrhous carcinomata. Those with large alveoli have a less abundant stroma and are called soft or medullary carcinomata. These two terms, "scirrhous" and "medullary," are purely clinical terms, and do not

imply a pathological difference, some carcinomata being scirrhus in one part and medullary in another.

Under normal conditions epithelium is an avascular tissue, no blood vessels penetrating between the cells. The same is found in carcinomata. The blood vessels run in the fibrous tissue stroma, and do not penetrate into the epithelial cell-masses. It follows that the blood vessels are always separated from the epithelial cells by an intervening layer of fibrous tissue. The blood vessels may be numerous or few; they are usually imperfectly formed, often being merely endothelium-lined spaces in the fibrous tissue. Sometimes, however, well-formed arteries and veins may be found in the stroma.

The cells of a carcinoma resemble, in general, those of the part in which it has originated. They are distinctly of an epithelial type with spherical or oval vesicular nuclei, showing a reticular arrangement of the chromatin. The cells lie in contact with one another, there being no intercellular substance.

If we examine the edge of a carcinoma we find that it is not sharply limited macroscopically or microscopically. The tumour shades off gradually into the surrounding structures, so that we find these structures embedded in the tumour and we find carcinoma cells in the surrounding tissues often far beyond the apparent limits of the growth. The structures embedded in the tumour show signs of degeneration and atrophy.

In the neighbourhood of the main mass of the tumour we may find separate nodules of carcinoma having the same structure as the primary growth. Further, we find similar nodules in the regional lymphatic glands and often in distant organs such as the liver, lungs, bones, etc. These metastatic tumours are more sharply limited than the primary tumour, and are more or less spherical in shape.

Macroscopically a carcinoma usually shows no definite shape, and appears as an infiltration rather than as a

definite swelling. The affected organ is usually hardened and, in the later stages, is fixed to the surrounding structures. Some carcinomata may appear as bulky swellings and may be apparently encapsulated. Carcinomata in the neighbourhood of free surfaces such as skin, mucous membrane, etc., are generally ulcerated, the ulcer having hard, raised edges. It is often impossible to tell, without a microscopical examination, whether a given ulcer is carcinomatous or inflammatory, and it is impossible to distinguish between a sarcoma and a carcinoma by macroscopical examination alone. Occasionally we meet with *melanotic carcinomata* arising from pigmented moles. It is not always easy to distinguish them from melanotic sarcomata.

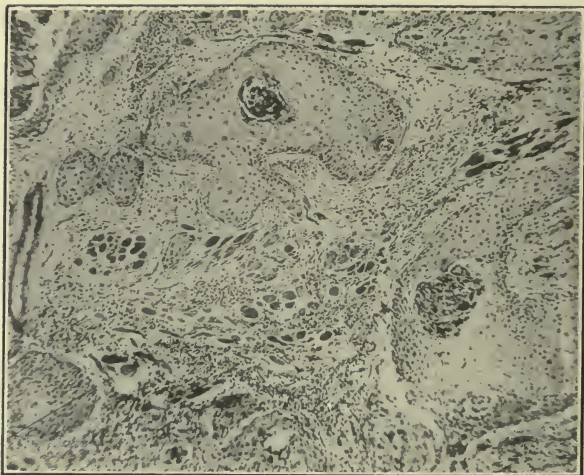
Carcinomata are subdivided into different species according to the type of epithelial cell of which they are composed. In the organism there are a large number of epithelial cell-types, but for practical purposes carcinomata may be divided into five species :

1. Squamous-celled carcinoma.
2. Columnar-celled carcinoma.
3. Spheroidal-celled carcinoma.
4. Syncytial carcinoma or syncytioma.
5. Endothelial cytoma or endothelioma.

The different types of carcinoma are usually distinct, but occasionally there may be mixed forms. In the squamous-celled carcinomata we include the carcinomata of organs containing transitional epithelium such as the bladder and pelvis of the kidney. The endothelial cytoma usually closely resemble the epithelial carcinomata, but some forms are divergent, and will be described separately.

Squamous-celled carcinoma.—Squamous-celled carcinoma (sometimes called *epithelioma*) is characterised by the large squamous cells resembling those present in normal squamous epithelium. The alveoli are usually large and irregular in shape. In a typical specimen the

cells nearest the fibrous tissue resemble those in the basal layer of the epidermis. As we pass towards the centre of the alveolus we notice successively the layers of prickle cells, the stratum granulosum, the stratum lucidum and, in the centre, the keratinised cells. Any of these layers may predominate or one or more may be wanting. In



— 50 μ

FIG. 52.

Squamous-celled carcinoma. Tongue. Several masses of squamous epithelial cells can be seen lying among the muscle fibres of the tongue, which are seen in transverse or oblique sections. The central cells of the larger masses are keratinised. There is an intense inflammatory, small-celled infiltration into the tissues of the tongue. See also figs. 53, 54, 72, 84.

some cases, for instance, the prickle cells are most conspicuous. In these cells the cytoplasm has a fibrillated structure, the fibrils passing from cell to cell and thus forming the intercellular prickles. In other cases the keratinisation may be in excess and the other layers much reduced. Again keratinisation may be entirely absent and the prickle cells inconspicuous. In the centre of

many of the cell masses the keratinised cells take the form of concentrically laminated bodies called "epithelial pearls" or "bird's-nest bodies." In other cases definite spaces lined by squamous epithelium are formed in the cell masses, the spaces being filled with desquamated epithelial cells. These spaces may be so large as to form cysts visible to the unaided eye. Leucocytes and mast cells are often found among the epithelial cells, sometimes in considerable numbers.



FIG. 53.

Squamous-celled carcinoma. Prickle cells. The cytoplasm of the prickles has a fibrillar structure, the fibrils radiating from the nucleus. The fibrils can be seen passing from one cell to the adjacent cells, thus forming the intercellular bridges or prickles. From a carcinoma of the tongue. (Drawing.)

The amount of stroma varies considerably. The remains of pre-existing structures such as muscle fibres, gland tubes, etc., are often found embedded in it. There is frequently also a large amount of inflammatory small-cell infiltration. Plasma cells and mast cells are often present in large numbers.

Macroscopically squamous-celled carcinoma usually appears as an ulcer with raised, hard edges, and there is

induration of the surrounding parts. In other cases there may be no ulceration, but the affected area is swollen and indurated. The regional lymphatic glands are affected, and there may be metastatic growths in distant organs.

Squamous-celled carcinoma affects any situation in which there is squamous epithelium. The commonest



FIG. 54.

Squamous-celled carcinoma. Epithelial pearls. From the skin of the back of the hand. This specimen shows an extreme degree of keratinisation, the keratinised cells forming laminated bodies (epithelial pearls) in the centre of the alveoli. See also figs. 52, 84.

sites are the cervix uteri, the lips, the mouth (especially the tongue), and the skin, especially on the face and limbs. It also occurs in the nose, pharynx (especially the tonsils), oesophagus, larynx, penis, clitoris, and scrotum. In rare cases it may arise in positions in which no squamous epithelium exists under normal conditions, e.g. in the gall bladder and the body of the uterus.

Rodent ulcer.—A special form of squamous-celled carcinoma of the skin is found in the condition known as rodent ulcer, or rodent cancer. This appears as a small, hard swelling which, sooner or later, ulcerates. It is found in the face, especially in the neighbourhood of the eye, rarely in other parts of the skin.

Microscopically it is characterised by alveoli filled with



FIG. 55.

Rodent ulcer. This is composed of small epithelial cells lying in alveoli, which are irregular in shape and often branched. There is no tendency to keratinisation and no formation of epithelial pearls.

small epithelial cells. The alveoli are irregular in shape, often showing blunt processes resembling the fingers of a glove. At other times the alveoli are small and angular. The cells do not show keratinisation. The tumour has no direct connection with the epidermis, which is thinned and stretched over it. The seat of origin is the epithelial cells of the hair follicles. The growth is exceedingly slow, often extending over many years. It is locally destruc-

tive, infiltrating and destroying all neighbouring structures, but it does not give rise to metastases.

Columnar-celled carcinoma.—Columnar-celled carcinoma is characterised by the presence of columnar epithelial cells, the greater number of which are arranged in tubes or spaces. It thus resembles the columnar-celled adenoma, but differs in the following respects :



FIG. 56.

Columnar-celled carcinoma. Rectum. This consists of tubes lined by columnar epithelial cells. The lining is irregular in thickness, being formed of one or more layers of cells. Within the tubes are seen desquamated cells and leucocytes. Contrast with fig. 25. See also figs. 57, 73.

(1) the alveoli are irregular in shape and size, and often contain more than a single layer of cells ; (2) it does not remain localised to its seat of origin, but is found infiltrating surrounding structures ; (3) if the growing part of the tumour be examined, small groups of columnar cells without definite arrangement will be found lying in the connective tissue spaces.

The stroma may be dense and fibrous, or it may be composed of a delicate reticular tissue.

Macroscopically these tumours may be soft and bulky, or they may appear as an ulcer with more or less surrounding induration. In the intestine they may appear merely as a stricture.

Columnar-celled carcinomata occur most commonly in the large intestine (especially the rectum and sigmoid),

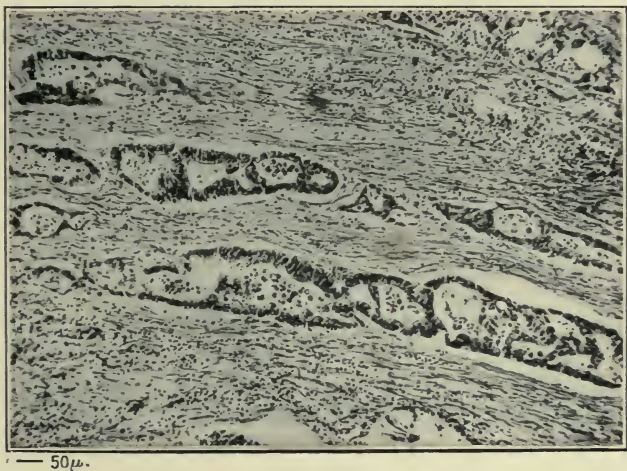


FIG. 57.

Columnar-celled carcinoma. Rectum. This section shows infiltration of the muscular coat, the carcinomatous alveoli being seen lying between the muscular fibres.

stomach, uterus, gall bladder, and breast. They are more rarely found in the testis, pancreas, ovary, kidney, and oesophagus.

Spheroidal-celled carcinoma.—The spheroidal-celled carcinoma is characterised by the spheroidal or polygonal shape of its constituent cells, which correspond to the secreting cells of glands. The cells show little disposition to any definite arrangement, usually being quite loose in the meshes of the stroma so that in frozen sections the

cells frequently drop out. Sometimes some of the alveoli contain lumina and the cells assume a cubical shape. The alveoli may be large or the stroma may be so abundant that they contain two or three cells only. The alveoli are of different shapes, often being long and narrow and containing a single row of epithelial cells. The stroma

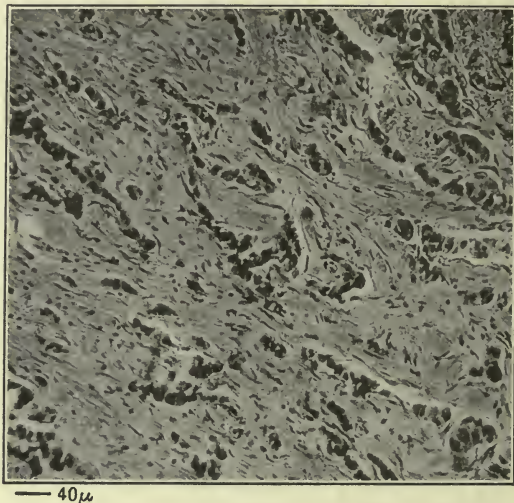


FIG. 58.

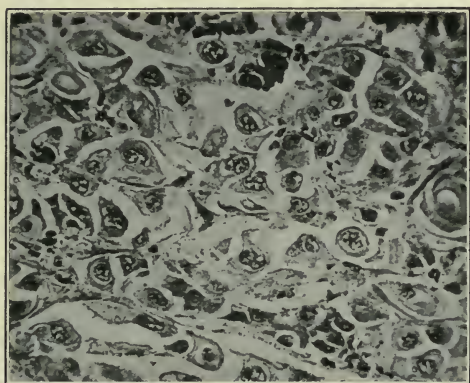
Spheroidal-celled carcinoma. Breast. This is a carcinoma of the type called "scirrhous." The epithelial cells are small and comparatively few in number. They lie in alveoli, which are little more than fissures in the fibrous-tissue stroma, there being often only a single row of cells. The stroma is abundant and formed of dense fibrous tissue. See also figs. 67, 75, 76, 78, 79, 85.

itself is usually well-formed fibrous tissue showing little or no inflammatory infiltration.

Macroscopically these tumours may be masses with ill-defined borders, or they may appear merely as a localised induration of the parts affected or, in slowly growing tumours—e.g. atrophic scirrhous—there may even be a shrinking of the affected part owing to the retraction

of the stroma. Ulceration is common in spheroidal-celled carcinomata of the breast and stomach. The regional lymph glands are affected early in the progress of the disease and metastasis is common.

Spheroidal-celled carcinoma occurs in the mamma, stomach, uterus, pancreas, liver, kidney, testis, ovary, oesophagus, adrenals, and thyroid; more rarely in other situations such as skin (sweat glands), tongue (mucous glands), salivary glands, and intestine.



— 25 μ

FIG. 59.

Primary carcinoma of the liver. This consists of cells which bear a general resemblance to hepatic cells, but are irregular in size and shape and are not arranged in columns. Contrast with fig. 28.

Colloid carcinoma.—A special form of either spheroidal-celled or columnar-celled carcinoma is the colloid carcinoma. Carcinomata of the thyroid often contain colloid, and in rare cases carcinomata in other situations may contain a substance with similar appearance and similar staining reactions. Such tumours are occasionally found in the breast and stomach. Far more frequently the tumours called colloid cancers are more properly called mucoid. Such tumours, which occur especially in the stomach and

intestines, appear in extreme cases as masses of a gelatinous slimy substance. In less marked cases small areas of a gelatinous appearance will be seen on the cut section of the tumour.

The production of the mucin in these tumours may be the result either of degeneration or of secretion. In the former case the tumour grows as an ordinary carcinoma, but the cells, becoming laden with mucin globules,



FIG. 60.

"Colloid" carcinoma. From a metastatic tumour in the spleen, the primary tumour being in the rectum. There is a large alveolus filled with structureless material (mucin), in which are lying groups of tall, columnar epithelial cells, which have become detached from the alveolar wall. In the epithelium can be seen clear globules of mucin.

degenerate and eventually disappear, so that the tumour appears as a network of fibrous tissue trabeculae, the meshes of which are filled with homogeneous material which gives the microchemical reactions of mucin. In the other case the cells, which are columnar in shape and bear a close resemblance to the goblet cells of the intestinal epithelium, actively secrete large quantities of mucin so that the alveolus is distended and eventually

ruptured, allowing the mucin to escape into the connective tissue spaces and lymphatics. The mucin thus escaped may be carried for a considerable distance away from the actual tumour.

Syncytial carcinoma, or syncytioma.—Occasionally in carcinomata and in other cytomata we meet with syncytia or multinucleated masses of protoplasm. In one type of tumour these syncytia form the characteristic elements. This tumour occurs in the uterus, and is known by the name *chorionepithelioma*, since the syncytial masses and the cells of which it is composed are derived from the chorionic epithelium of the placenta (i.e. from foetal tissue). The tumour arises after a pregnancy which has been, in the majority of cases, abnormal, a frequent antecedent being the hydatidiform mole. In the formation of the normal placenta the chorionic villi penetrate into the uterine blood sinuses so that the chorionic epithelium comes to lie in contact with the maternal blood. In hydatidiform mole there is considerable proliferation of the chorionic epithelium and oedematous degeneration of the stroma of the villi. Associated with these changes we find an increased power of growth of the epithelium which continues to grow long after the expulsion of the embryo. Both in the normal placenta and in the mole portions of the villi are apt to become detached and carried in the circulation to lodge as emboli in the lungs or elsewhere, but these detached portions do not grow, but are quickly absorbed. In the chorionepithelioma we find a more advanced stage of this condition. We have an infiltrating tumour causing destruction of the uterus and giving rise to metastatic growths. The tumour contains as its characteristic elements syncytial masses sometimes irregular in shape resembling multinucleated giant cells and sometimes forming long irregular ribbon-like strands of multinucleated protoplasm. Associated with these are groups of polygonal cells. The syncytial masses resemble the

chorionic syncytium and the polygonal cells resemble the Langhans cells of the chorionic villi. These two elements are closely related and intermediate forms are seen. The syncytia and polygonal cells are embedded in blood which, for the most part, is clotted, and there is often extensive necrosis. The tumour has no definite stroma

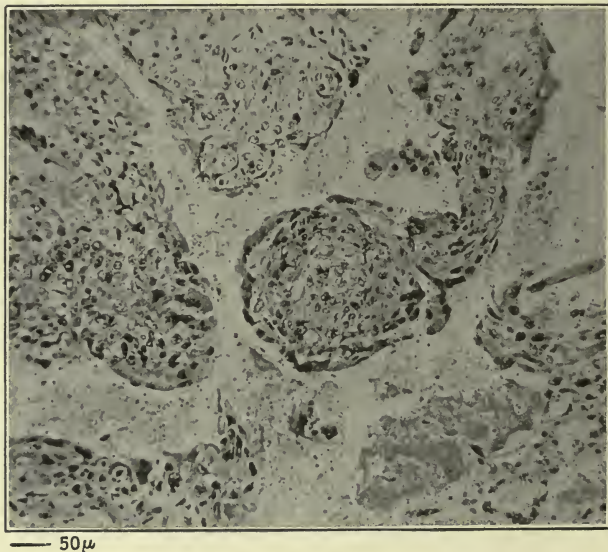


FIG. 61.

Chorionepithelioma. From a metastatic nodule in the liver. There is a large blood space projecting into which are several cell masses. The cells in these masses are mainly polygonal in shape, but the surface layer next the blood is formed of long, multinucleated, syncytial structures.

and no blood vessels of its own. It is mainly confined to the interior of the uterine blood vessels, but may spread for a little distance into the muscle, infiltrating along the track of the blood vessels. By its growth the tumour destroys the wall of the blood vessel in which it lies, and thus gives rise to extensive haemorrhages.

Macroscopically the tumour closely resembles a mass

of blood clot. It is very soft and friable. Metastatic tumours may be found in the vagina, lungs, and liver, occasionally in other situations. They are confined to the interior of the blood vessels.

Similar tumours are occasionally found apart from pregnancy, and have been described as arising in teratomata both in males and females. Their existence in these situations is not fully explained.

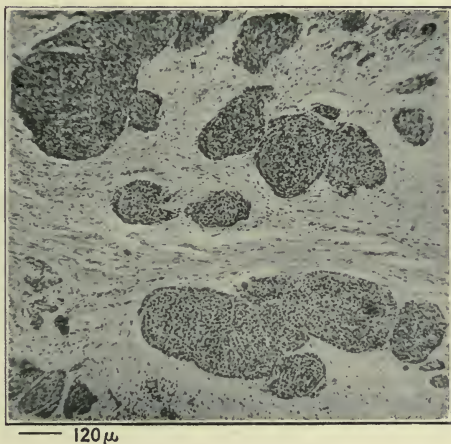


FIG. 62.

Endothelial carcinoma. Parotid. This tumour consists of alveoli filled with small cells. Under a higher magnification these cells could be seen to have the characters of endothelial cells. In other parts of the tumour some of the cell masses contained one or more lumina.

Endothelial cytomata (endotheliomata).—Endothelial cytomata resemble carcinomata in that their characteristic elements are cells which lie in contact with each other. Endothelial cells are flat cells polygonal in shape, with a small round or oval nucleus and a relatively large amount of cytoplasm. When seen from the edge they appear spindle-shaped. We sometimes find tumours with an alveolar structure in which the alveoli contain cells of

these characters. The cells may completely fill the alveoli, or there may be a central lumen. The cells may be definitely spindle-shaped so that, at first sight, the tumour resembles an alveolar spindle-shaped sarcoma. The cells, however, lie loosely in the alveoli without any intercellular substance. Such tumours can be rightly called endothelial carcinomata.

Frequently, however, tumours which we must regard as of endothelial origin show the characters of ordinary

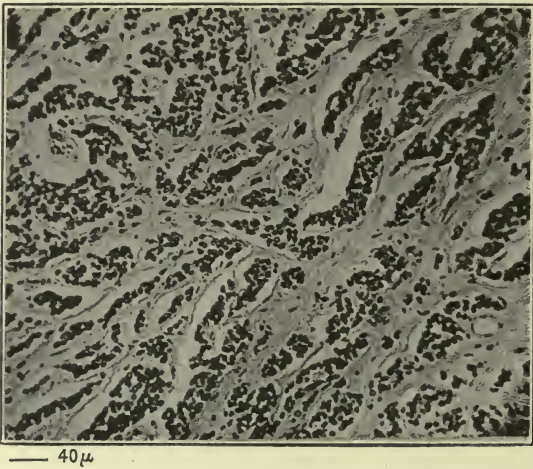


FIG. 63.

Primary carcinoma of the pleura. This is hardly to be distinguished from an ordinary spheroidal-celled carcinoma. Compare with fig. 58.

squamous, columnar, or spheroidal-celled carcinomata. This is the case in the primary carcinomata of the serous membranes, especially of the pleura and peritoneum. Macroscopically these tumours appear as a diffuse thickening of the membrane, sometimes involving the whole surface, rather than as distinct nodules. The tumours are not confined to the serous membrane, but infiltrate the surrounding structures and give rise to metastases.

In other cases the endothelial proliferation has an obvious relation to the blood vessels or lymph vessels, and the proliferation may be inside or outside the vessel. These are usually diffuse tumours. In some cases there is proliferation of the endothelium covering the small vessels, forming a mantle of several layers of cells. Such tumours are often called *angiosarcomata*, but are better called *perivascular endotheliomata*. The areas between the



FIG. 64.

Primary carcinoma of the peritoneum. This has a somewhat close resemblance to a squamous-celled carcinoma. It consists of small alveoli filled with flattened cells resembling squamous cells. Many of the alveoli show structures resembling epithelial pearls. Compare with figs. 52, 54.

separate vessels are occupied by necrotic cells mixed with blood. The tumours are very haemorrhagic and often, to the naked eye, appear like haemorrhages. They may occur in the brain, kidney, uterus, or other situations.

The part which the blood vessels play in these tumours is uncertain. In some cases at least they have the same origin as the surrounding endothelial cells, i.e. some of the endothelial cells become specialised to form the capillaries in the same way that the epithelial cells of a

columnar-celled carcinoma form epithelial tubes. In other cases it is possible that the vessels are the original blood vessels of the part in which the tumour originated, the proliferation taking place in the surrounding lymph space. Tumours which show a perivascular distribution of their characteristic cells are not all of the same nature.

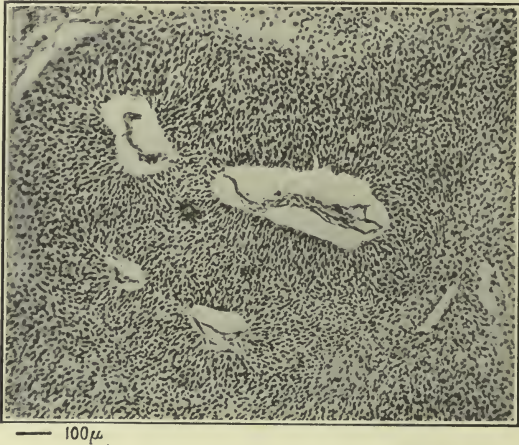


FIG. 65.

Perivascular endothelioma (angiosarcoma). Uterus. Several vessels are seen each surrounded by a many-layered mantle of cells arranged more or less radially. The endothelium of the blood vessels has shrunk away from the surrounding cells. The blood vessels consist of an endothelial coat only.

Endothelial cytomata are apt to vary in structure in different parts. One part of the tumour may resemble a carcinoma, while another part has more the appearance of a sarcoma.

The tumour known as a large, round-celled alveolar sarcoma, which resembles a carcinoma very closely, is probably an endothelial cytoma.

CHAPTER VII

THE GENERAL MORPHOLOGY AND RELATIONSHIPS OF TUMOURS

HAVING considered the various kinds of tumours individually, it will be convenient to discuss some points in the morphology of tumours in general before proceeding to consider the physiological aspects of tumour growth.

Tumours in general tend to grow equally in all directions and thus to assume a spherical shape. This is well seen in tumours which originate in the interior of homogeneous soft organs—e.g. adenomata of the liver, kidney, etc., myomata of the uterus; also metastatic carcinomata and sarcomata of the liver and lungs. Actually, however, the spherical shape is frequently departed from owing to various causes. The surrounding tissues, by their different degrees of consistency, have a marked effect in determining the shape of tumours, growth occurring in the direction of least resistance. Thus, tumours lying among the limb muscles and tendons assume an elongated or ovoidal shape, and the neighbourhood of resisting structures, such as bones or dense fasciae, has a considerable influence on the shape of a tumour growing near them.

Tumours originating in the neighbourhood of a cavity or free surface tend to project outwards. Such a tumour, if it has a broad base, is said to be sessile, while if the base is contracted so that the tumour hangs from it as from a stalk, the tumour is said to be pedunculated. Pedunculated tumours such as fibromata, myomata,

sarcomata, growing inside cavities such as the nose, alimentary canal, uterus, etc., are sometimes called polypi. Not all polypi, however, are of the nature of a tumour. Some tumours growing on a surface are apt to have a villous or warty structure which, in extreme cases, may recall the appearance of a cauliflower. Such a form

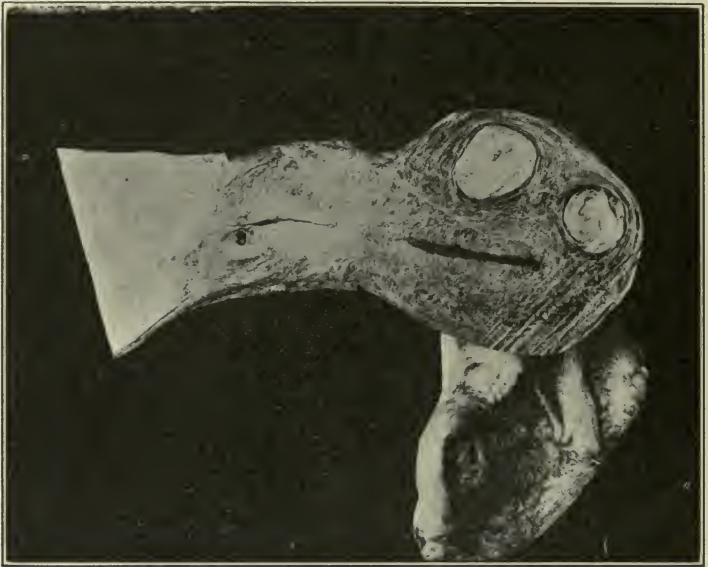


FIG. 66.

Encapsulated tumour. Myoma of the uterus. A longitudinal section of the uterus, showing two myomata. These are spherical bodies sharply marked off from the surrounding muscle. Contrast with fig. 67.

of growth is found in papillomata and carcinoma, especially of the cervix uteri and glans penis.

Many tumours, especially the cytomata, cannot be said to have any definite shape. They have no definite boundaries, and exist as infiltrations of the affected organs rather than as distinct nodules.

The consistency of a tumour naturally varies with

the nature of its constituent elements. Tumours show any degree of hardness between the stony hardness of the ivory osteomata and the semi-fluid condition of the myxomata. Pathological changes in the substance of the tumour will also influence the consistency, e.g. fatty degeneration, calcification, haemorrhage, cyst formation, etc.

Coming now to the minute structure, we have seen that a tumour may consist of any kind of tissue. We can in general distinguish between two constituents of the

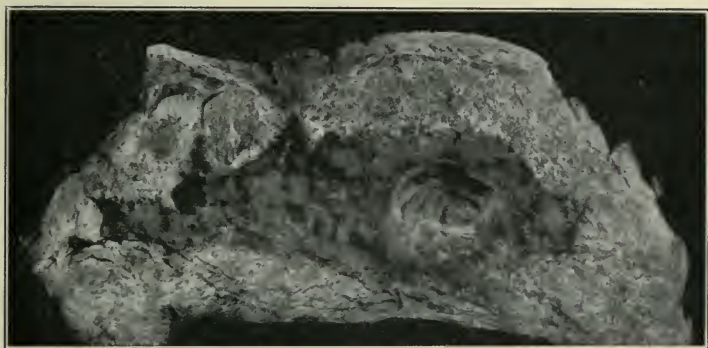


FIG. 67.

Infiltrating tumour. Carcinoma of the breast. The tumour is seen as a dark mass with irregular outlines lying among the surrounding fat. In the right side there is a cyst which has been cut across. Above is seen the skin with the nipple. The nipple is depressed. Contrast with fig. 66. Compare fig. 74.

tumour, namely, the essential elements which give the character to the tumour (*parenchyma*) and the vascular connective tissue, by means of which the tumour is nourished (*stroma*). Sometimes, especially in fibromata and sarcomata, we cannot distinguish these two constituents, although even in fibromata the connective tissue surrounding the blood vessels sometimes has characters different from those of the fibrous tissue forming the bulk of the tumour. The relation of the essential

elements or parenchyma of the tumour to the stroma is, as a rule, similar to that obtaining in the organ of origin. Thus, in lipomata we have small lobules of fatty tissue, each having its own afferent and efferent vessels; in adenomata the relation between the epithelium and the blood vessels resembles that in the organ of origin, and in chondromata, as in normal cartilage, the blood vessels are confined to the fibrous tissue investing the cartilaginous nodules.

In some tumours the parenchymatous elements have a definite perivascular arrangement. This arrangement is not characteristic of one type of tumour only, but may arise in different ways.

1. The vessels themselves may be formed from the parenchymatous elements in endothelial cytomata. Thus, a solid column of endothelial cells may show a capillary in the centre, the endothelium of the capillary being formed from the surrounding cells (*angeioendothelioma*).

2. Proliferation may take place in the endothelium of the perivascular lymph channel. In this case the endothelium of the vessel will be surrounded by a zone of fibrous tissue which separates it from the surrounding proliferating cells (*perivascular endothelioma*).

3. Cytomata may show a tendency to spread along the perivascular spaces.

4. In spindle-celled sarcomata the spindle-cells may show a definite relation to the blood vessels being arranged parallel or radially to them, or at an intermediate angle.

5. In some carcinomata and sarcomata extensive necrosis of the parenchyma may take place, involving especially the cells at a distance from the blood vessels. Each blood vessel and its accompanying stroma is thus left with a surrounding mantle of proliferating cells.

The amount of stroma and the degree of vascularity vary considerably. In some cases the fibrous tissue may be in great excess, and may even appear to be the dominant feature of the tumour. In other cases there may be

little fibrous tissue or the blood vessels may be very numerous or excessively dilated. The distribution of the stroma in a tumour varies. Often there is no definite arrangement, while at other times the stroma divides up the tumour into more or less distinct lobules formed by septa passing in from the periphery of the tumour (lipomata, myxomata, chondromata).

Some tumours are definitely encapsulated and lie in a distinct fibrous-tissue sheath and, when the sheath

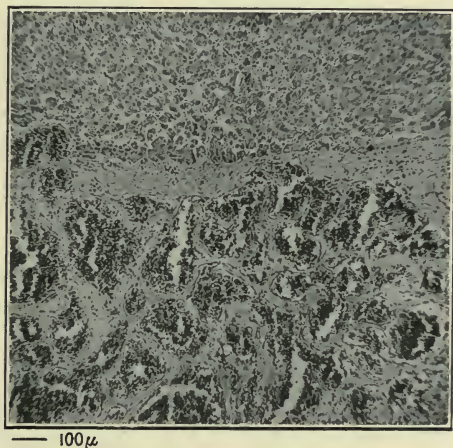


FIG. 68.

Cavernous angioma of the liver. The tumour is bounded by a fibrous tissue capsule which is continuous with the connective tissue of the liver. See also fig. 33.

is opened, can easily be shelled out. Such tumours have a smooth outer covering of connective tissue (*capsule*) which is connected with the surrounding sheath only by the blood vessels which pass from one to the other. The sheath is formed by condensation from the tissues surrounding the tumour. Other tumours which show a distinct capsule of fibrous tissue are not contained in a separate outer sheath, but the capsule is closely connected with the surrounding tissues. In others, again, the stroma

is directly continuous with the connective tissue of the organ in which the tumour is situated, and there is no definite boundary to the tumour.

The significance of the stroma differs in the three cases. In the encapsulated tumours which can readily be shelled out of the sheath the stroma must be regarded as an integral part of the tumour itself, although it is subsidiary to the essential elements. It grows *pari passu* with the parenchyma and, with it, forms a connected whole. In the second group of cases the stroma of the tumour must also be considered as an integral constituent. In the third case, however, the conditions are different. Here the stroma is not an integral part of the tumour, but consists of the modified remains of the tissues which have been penetrated by the tumour. This may be inferred by the presence in the stroma of gland tubes, muscle fibres, nerves, etc., derived from the organ in which the tumour is growing.

The *blood vessels* of a tumour are imperfectly formed. They are often merely endothelium-lined spaces in the stroma. Apart from the teratomata definite arteries and veins are not found except when they are the remains of the pre-existing vessels which have become embedded in the tumour. *Lymphatics* may occur in tumours, but *nerves*, except in the teratomata, are not found, except as the included remains of pre-existing nerves.

The parenchyma of a tumour may, or may not, be in continuity with the surrounding structures. It may be of the same character as those of the organ of origin, or it may have different characters.

In a metastatic tumour the structure usually corresponds closely with that of the primary tumour.

We have mentioned that, in our classification, each group shows certain characters which distinguish it from other groups. In other words, the tumours in each group are more closely related to one another than they are to tumours in other groups. We also mentioned that inter-

mediate forms of tumour exist between the different groups. This is inevitable in any system of classification, owing to the want of any sharp distinction between the various units of which the body is composed. We find that tumours are related to one another in various ways.

If we consider any individual type of cell and the corresponding tissue, we find that we have a complete series of tumours commencing with the pure cytoma, passing through the compound cytoma to the corresponding histioma. Thus we have spindle-celled sarcoma, fibrosarcoma, and fibroma, and so for every other kind of cell. In the case of the tumours corresponding to the blastocytes or indifferent cells we have blastocytoma, composed of indifferent cells which give rise to differentiated cells and tissues; teratoid histioma, composed throughout of definite tissues of various kinds; and teratoma in which definite organs are present. There is no sharp line delimitating these three forms of tumour corresponding to a particular cell-type. They are closely related, but the characters of the histioma and the pure cytoma are quite different, the characters of the compound cytoma being intermediate.

There are also relationships between tumours corresponding to different cell-types. Thus all the desmوماتа, except the gliomata and chórdomata, are closely related, and it is impossible to draw sharp lines of distinction between them. Mucous tissue and fibrous tissue merge into cartilage, bone, and fat, and the same is the case with the corresponding histiomata. Similarly it is impossible to draw a sharp distinction between the different types of epithelial histiomata. The same may be said of the different types of sarcomata and carcinomata.

Another kind of relationship exists between the supporting tissue histiomata and the histiomata of special tissues. Thus, as we have seen, the fibroma and the adenoma of the breast gradually merge into one another. Again, the blood vessels of a fibroma may become dilated

into cavernous spaces, so that there is no sharp distinction between an angeiectatic fibroma and an angioma. Also there are all grades of proportion between the muscle and fibrous tissue in a myoma. Again, in the blastocytomata we may have epithelial cells, myxocytes, chondrocytes, myocytes, etc., but we may have a tumour containing all these except the epithelial cells, and we have a series of tumours of decreasing degrees of complexity until we come to a tumour consisting of one type of cell or tissue only. On the other hand, we may have blastocytomata showing a gradually increasing proportion of epithelial cells until they merge into the carcinomata or adenomata.

We thus see that tumours are related to one another in various ways. They are also related to other conditions not included in the category of tumours, especially to the conditions of progressive hypertrophy and gigantism which might be described as a diffuse tumour-like formation involving a whole organ or group of organs.

CHAPTER VIII

THE ORIGIN OF TUMOURS

The Rudiment of Origin.

IN considering the physiological aspects of tumour formation the first question that arises is, What is the rudiment from which the tumour originates? We have seen that tumours are composed of cells or tissues resembling those normally present in the body, and we can safely conclude that the original rudiment consists of similar elements.

There are three possible sources of these rudiments : (a) they may be extrinsic in origin, i.e. derived from outside the organism ; (b) they may be cells or complexes sequestered by a process of malformation during development ; (c) they may be the tissues forming part of the structures at the seat of origin.

(a) The extrinsic origin of tumours was an old hypothesis. They were thought to be something foreign to the body, but grafted on to it. We now recognise that this source of tumours in a particular animal is possible only when the rudiment consists of portions of a tumour which has itself originated in an animal of the same species. Tumours can, in fact, be grafted from one animal to another of the same species, and it has been proved that the tumour thus originating is derived from the actual elements of the grafted tumour. It is not necessary to graft the whole tumour ; a few cells, perhaps even a single cell, is sufficient to form the rudiment of the new tumour. This process of grafting is exactly

comparable to the grafting which occurs naturally in metastasis, which we consider in the next chapter. In metastasis portions detached from a tumour may be carried by the circulation to distant parts of the body, and may there serve as rudiments for the origin of metastatic tumours.

With the possible exception of syncytioma, whether or not such a grafting between two individuals ever occurs in man is an open question. While a tumour, e.g. a carcinoma, can by contact give rise to a new tumour in the same patient, such a transference as between two individuals is extremely rare, even if it occurs at all. Carcinoma of the cervix uteri is an extremely common form of tumour, whereas carcinoma of the glans penis as a result of sexual connection is not known certainly to occur. The question is an exceedingly difficult one to answer, as, owing to the fact that transference by contact must almost always concern surfaces covered by squamous epithelium, the characters of the two tumours would be the same whether the second tumour arose by inoculation or whether it was an independent growth altogether. There are, however, some cases where there is undoubted transference by contact, but in these cases it is open to question whether the growths concerned are to be considered true tumours or not. Ordinary skin warts can be transferred from one person to another, and the so-called venereal warts (*condyloma acuminatum*) are highly contagious. It is quite impossible to draw a sharp distinction between these warts and papillomata, which are undoubted tumours. The same is the case in the growths which occur in the penis and vulva of dogs. These have the histological structure of lymphocytomata, but are highly contagious. They are transferred by sexual connection, and may give rise to a serious epizootic. Some observers claim that these are true tumours, while others state that they are infective granulomata and that their mode of growth differs from that of the true tumours. If we take

into account the recent experiments on the grafting of tumours in animals, we cannot deny the possibility of tumours being conveyed by contact in the natural condition, and we cannot say that a particular form of growth is not a true tumour merely because it is contagious.

(b) We come now to the second possibility which states that the rudiment of origin may be composed of cells or

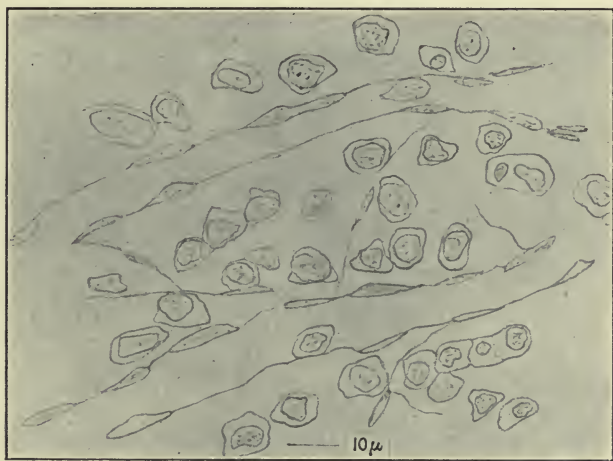


FIG. 69.

Lymphocytoma. From the vulva of a bitch. Two capillaries are seen, and between them are cells resembling the mother cells of lymphocytes, supported by a delicate reticular stroma. (Drawing.) Compare with fig. 51.

complexes which have been sequestered during development. This theory was greatly elaborated by Cohnheim, who attempted to attribute the origin of all tumours to this kind of rudiment. According to him, tumours could not arise from the normal tissues of the body, but always start in a group of cells which, separated during an early stage of development, took no part in the formation of the normal structures, but retained their embryonic charac-

ters. The only structures completely fulfilling these conditions are, if we except the ovarian ovum, the pigmented moles. These moles are formed during development, and take no part in the formation of the skin, retaining their undifferentiated and embryonic characters throughout life.

A pigmented mole is an area of skin in which, immediately beneath the epidermis, there are groups of large, round,



FIG. 70.

Pigmented mole. In the papillae and subjacent corium are groups of large epithelioid cells. Here and there are masses of pigment.

or polygonal cells. These cells may completely replace the dermal papillae, and they may be found in the epidermis itself. Some of the cells are pigmented, while others are free from pigment. The cells are grouped in more or less distinct alveoli. The origin of these cells is uncertain. By different authors they have been attributed to an endothelial, epithelial, or connective tissue origin. The origin of the cutaneous pigment is similarly uncertain. Pigment is found in the deeper layers of the

epidermis and in the subjacent cutis. According to some the pigment is formed in the epithelial cells and passes from them into the intercellular spaces, and so into the cutis, where it is taken up by wandering cells. According to others the pigment is formed in the cutis cells, and is taken up by the epithelial cells. Others, again, think that the epithelial and cutis pigments are independent. The evidence seems to be distinctly in favour of the first view, that the pigment is of epithelial origin, and the same seems to be true of the cells of the pigmented mole. Such moles frequently give rise to tumours, especially melanotic sarcomata and carcinomata.

Apart from the actual demonstration of such rudiments we can infer that other tumours have this mode of origin. This is especially the case with regard to the complex tumours, the blastocytomata, and teratomata. In the blastocytomata of the kidney (p. 99), for instance, we recognise the presence of cells which, themselves undifferentiated, give rise to epithelium; muscle, cartilage, bone, and other forms of differentiated tissues. It seems clear that these undifferentiated cells correspond to, and are derived from, the undifferentiated cells which, in the embryo, give rise to the normal structures—bone, muscle, Wolffian body, and kidney—in the same region. The earlier in embryonic life such a rudiment was sequestered, the less differentiated will be the cells, and hence the more complex the tumour arising from them. We may notice that in some of these tumours the epithelial tubes may develop into glomeruli with Bowman's capsule, etc., just as in the normal kidney, but such glomeruli do not contain the normal tuft of capillaries.

The *teratomata* contain (p. 45) various organs such as skin, teeth, brain, etc., and, as we can hardly suppose that such structures can arise from normal tissues, we must suppose that they arise from a sequestered rudiment the cells of which retain their power of differentiation and of developing into different organs. What the nature

—of these rudiments is, however, not clear, and none of the many theories is altogether satisfactory. No one theory is adequate to explain the origin of all teratomata. It is impossible to consider fully the pros and cons of all the different theories, but we may briefly review the more important of them.

The teratomata of the nasopharynx can be safely attributed to a rudiment derived from fission of the embryonic area (anterior or posterior dichotomy). These masses project from the mouth and show all gradations from a more or less fully formed body with limbs, etc., to a teratoma consisting of a heterogeneous collection of organs and to a blastocytoma in which the cells retain to a large extent their undifferentiated characters. Similarly the teratomata of the sacro-coccygeal region may be attributed to fission of the embryonic area. These tumours are always congenital.

The theories relating to the origin of ovarian teratomata may be divided into two groups: those dependent on, and those independent of, fertilisation. We can leave out of account any theory which depends on fertilisation in the patient in whom the teratoma appears. Fertilisation of an ovum in the ovary gives rise to ovarian pregnancy, and many ovarian teratomata arise independent of fertilisation. If fertilisation is concerned at all it must have been effected in the previous generation, i.e. at the same time as the fertilisation of the ovum from which the patient bearing the teratoma was developed. Such theories suggest (1) the fertilisation of a polar body, (2) the post-fertilisation of a primordial ovum of the embryo by spermatozoa which had remained dormant after the fertilisation of the ovum. The theories independent of fertilisation suggest as rudiments of origin (3) the sequestration of portions of ectoderm in connection with the Wolffian duct, (4) the ovarian ovum, (5) the follicular cells of the Graaffian follicle, (6) primordial germ cells, (7) sequestered blastomeres.

One difficulty about the theories which do not involve fertilisation is the colour of the hair in teratomata. This may be quite different from the colour of the patient's hair, whereas, if the teratomata were produced by a process akin to parthenogenesis or budding, we should expect the colour of the hair to be identical in the patient and in the tumour. It is possible, however, that the different conditions in which the hair grows—in the one case exposed to the air, and in the other enclosed in a cavity full of debris and fatty material—may account for the difference in colour.

If we briefly consider the different theories we can reject the first, as it will not account for the presence of several teratomata—five or more—in the same ovary. The second theory requires that the spermatozoa survive and retain their activities until the primordial ova are produced, that there should be a premature maturation of the primordial ovum or of several primordial ova, and that these fertilised primordial ova should remain dormant throughout development until after birth. These suppositions seem very unlikely.

The third theory may be disregarded, as it will not account for the various structures in a teratoma; moreover, the Wolffian duct has no connection with the ovary itself, whereas teratomata arise within the organ. The intraovarian position of the teratomata is in favour of their origin from the ovum or follicular cells, and these tumours are often associated with follicular or proliferating cysts. Against the origin from the ovum, however, we have the fact that nothing approaching parthenogenesis is known to occur in the higher animals. The sixth and seventh theories apply also to teratomata in situations other than the ovaries. If teratomata are derived from primordial germ cells we should have to explain their occurrence in positions other than the sex glands by assuming that the primordial germ cells had wandered from their normal situation. On the other hand, if we

attribute the teratomata to sequestered blastomeres, it is difficult to explain the great frequency of their occurrence in the ovary as compared with the testis and other situations. Finally, sequestration of ectoderm is insufficient to explain the origin of teratomata. Such a sequestration gives rise to the cysts we have described as sequestration cysts.

We thus see that there is no satisfactory theory to explain the origin of teratomata, and the nature of the rudiment from which they arise must be left undecided.

Apart from sequestered rudiments which retain their embryonic characters as postulated by Cohnheim, we know of numerous rudiments which, while foreign to the part in which they lie, yet in themselves have developed along normal lines. Thus, during the development of the long bones, especially in cases of rickets, small nodules of typical cartilage are often sequestered and take no further part in normal development. Such nodules may give rise to chondromata and cartilaginous osteomata. Again, sequestered portions of pancreas have been found in the wall of the stomach or duodenum, and rudiments of Wolffian body origin, showing the structure of the adrenal cortex, have been found in the kidney, liver, retroperitoneal tissue, broad ligament of the uterus, spermatic cord, etc., and may give rise to tumours, adenomata, or carcinomata, having the characters of adrenal tumours. Sequestered rudiments of squamous epithelium may be found in the skin, palate, tonsils, etc., and sometimes in other situations, such as the broad ligaments. Also in the neck we may have rests derived from the branchial clefts or arches, and these may give rise to carcinomata or other tumours. Tumours may also arise in connection with the remains of the thyro-glossal duct.

Apart from these demonstrable rudiments it is quite possible that many tumours arise from similar rudiments which are not demonstrable. The actual structures from

which a tumour originates can only in very rare cases be detected, since, by the time the tumour comes under observation, it has grown to such an extent that the actual point of origin is indistinguishable.

Another way in which tumours may arise as a result of maldevelopment is the following. During the development of an organ there may be an arrest of development of the parenchyma in a localised area accompanied by



FIG. 71.

Adrenal tumour (hypernephroma) of the kidney. The tumour consist of groups of epithelial cells lying in a very delicate stroma. The cells are highly vacuolated with small nuclei, resembling closely the normal cells of the adrenal cortex. The stroma consists of little more than capillaries.

increased development of the stroma, either fibrous tissue or blood vessels. When the organ is fully developed this area will appear as a nodule of fibrous tissue, or of blood vessels. Such a nodule may assume progressive growth and form a definite tumour, or it may remain *in statu quo* throughout life. This kind of tumour is called "*hamartoma*" (ἀμαρτάνω, to fail). Examples are seen in the cavernous angiomas of the liver and in the fibromata of the medulla of the kidney.

(c) The normal tissues are suggested as rudiments of origin for tumour formation by the fact that the constituent elements of tumours resemble, in the great majority of cases, those of the part in which the tumour has originated, and there is no doubt that some tumours do originate directly from the normal elements of the

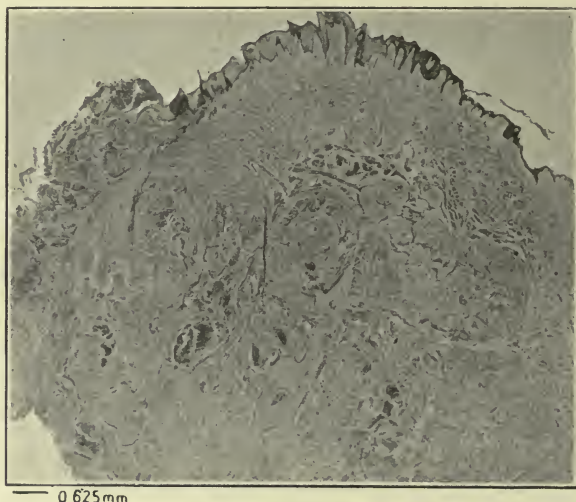


FIG. 72.

Squamous-celled carcinoma of the tongue, showing its origin from the mucous membrane. At the extreme right of the upper part of the section the normal mucous membrane of the tongue is seen as a thin line. In the middle of the upper surface the epithelium is much thickened and is in a papillomatous condition. On the left side the mucous membrane is destroyed and replaced by epithelial cell masses which have, from this part, invaded the muscular substance of the tongue as seen in the lower part of the section.

part. The epithelium of a papilloma is directly continuous with the neighbouring epithelium, and the same may be said of some adenomata and carcinomata, especially squamous and columnar-celled carcinomata. Angeliomata also are directly continuous with normal blood or lymph vessels and some fibromata, sarcomata, osteomata,

chondromata, etc., are also in direct continuity with the neighbouring tissues. In other cases the tumour may arise from cells which have been separated from their normal connections as the result of inflammatory changes or injury.



FIG. 73.

Columnar-celled carcinoma of the rectum, showing its origin from the mucous membrane. The mucous membrane in the left side of the section is normal and its lower limits are well defined by the muscularis mucosae. On the right side the muscularis mucosae has disappeared and epithelial tubes are seen passing from the mucous membrane and infiltrating the subjacent tissues.

The origin of tumours from normal tissues is also suggested by the fact that the cells of a tumour display, to some extent, the same physiological characters as those of the part in which the tumour has arisen (p. 175).

Numerous experiments have been carried out in this connection to determine whether cells and tissues separated from their normal connections are capable of

giving rise to tumours. We have seen that in the grafting of tissues the grafts, under favourable circumstances, continue to live and functionate in their new position. Such grafts do not grow beyond normal limits and are permanent only if they are of functional utility. Experiments to investigate the origin of tumours have been conducted by introducing portions of foetal or adult tissues into blood vessels, serous cavities, subcutaneous tissue, etc. Some such grafts, especially if composed of foetal tissues, may grow for a time and form distinct nodules. They, however, lack the progressive growth which is characteristic of tumours and are eventually absorbed. The only cases of successful production of a tumour are those in which the graft itself is derived from a tumour.

Some tumours are composed of tissues foreign to the part in which they arise. This does not necessarily imply that they arise from sequestered rudiments, since we have seen that, within limits, it is possible for one tissue to arise from another. Hence the presence of cartilage in a tumour may be explained by its arising from fibrous tissue, or other forms of supporting tissue, by metaplasia. The presence of squamous epithelium in tumours of the breast, lungs, gall bladder, or uterus may be attributed to metaplasia of the normal epithelium. In fact, even in the colon we occasionally find a carcinoma in which typical squamous cells occur together with the more common columnar cells.

The rudiment of origin may be small or large. Metastatic cytomata grow from a rudiment which is capable of passing through the capillaries, and hence cannot be larger than one or two cells, and it is quite possible that primary tumours arise from an equally small rudiment. There is little doubt that the great majority of tumours arise from a rudiment consisting of a few cells or a small cell-complex. It is this fact that makes it difficult to detect the nature of the rudiment of origin.

On the other hand, cases are known, especially in the breast and liver, where a tumour, or tumour-like growth, starts simultaneously in the whole of the organ. Thus we may have diffuse carcinosis or sarcosis involving the whole of the breast or liver, or we may have a diffuse overgrowth of the capillaries (angeiectasis) involving a whole organ as in macroglossia, or we may have, as we have mentioned, a diffuse overgrowth of the fibrous or muscular tissue or a general progressive hypertrophy.

Between these two extremes there are intermediate stages. The general characters of tumours point to their origin from minute rudiments, diffuse and semi-diffuse forms being rare.

The tumour may start from a single rudiment or from several, the tumours arising from each rudiment coalescing to form a single tumour. This multicentric origin is sometimes found in carcinoma.

Occasionally the rudiment of origin of a tumour may be the elements of a pre-existing tumour. Thus a carcinoma may start in an adenoma or a teratoma. We shall return to this point.

Sites of Origin.

An outstanding fact in the pathology of tumours is the great frequency with which they arise in the female genital organs and breast. It is due to this fact that tumours are more common in females than in males. These organs are characterised by the fact that the elements composing them are capable of great variations in proliferative capacity and throughout the period of sexual activity—at puberty, during menstruation and pregnancy—there are periodical active proliferative changes going on. After the menopause tumours are not so common in these organs, and pre-existing tumours may cease growing and retrogress. The corresponding male organs are rarely the seat of tumour-formation.

Another tissue which is characterised by great proliferative capacity is the squamous epithelium of the skin and mucous membranes, and this is one of the most frequent seats of tumour growth. Similarly the epithelium of the alimentary canal is continually being shed and renewed. The connective tissue generally is possessed of a great capacity for proliferation and is a frequent source of tumours.

On the other hand, when we come to consider tissues which have little proliferative capacity, we find that they rarely give rise to tumours. Such are especially the nervous tissue and striated muscle. Smooth muscle, apart from the uterus, is also a rare source of tumours. Gland and duct epithelium, apart from the mammary gland and ovary, are rare sources of tumours compared to surface epithelium.

We come, then, to the conclusion that the most frequent sources of tumour growth are those tissues the cells of which show the greatest proliferative capacity normally, and, if we consider a single tissue, e.g. smooth muscle, we find that it most frequently gives rise to tumour formation in those situations in which it normally shows the greatest proliferative power.

Apart, however, from this question of proliferative capacity, there are other influences, e.g. external influences, which determine the sites of tumours. These we shall consider when we discuss causation.

Some organs are very rarely the seat of tumour growth. The muscles, for instance, are rarely the seat of tumours either of muscular or connective tissue origin, and they are very rarely the seat of metastatic tumours. The spleen, again, is very rarely the seat either of primary or metastatic tumours. Also tumours rarely arise in the small intestine while they are common in the large intestine and in the stomach. We know of no explanation for these facts.

CHAPTER IX

THE GROWTH AND LIFE HISTORY OF TUMOURS

Growth.

THE next point to consider is—how does the tumour grow ? what is its life history ?

We have seen that, in the great majority of cases, the rudiment from which a tumour arises is a minute group of cells or a cell-complex which may form part of the normal tissues or may be sequestered during development. There are two possibilities to be considered as to the mode of growth of the tumour from the rudiment : (1) the tumour may enlarge by successive additions to it of elements derived from the surrounding structures ; (2) the tumour may enlarge by proliferation of its own cells. The first of these methods, which strictly speaking is not growth at all, is called centripetal or appositional growth ; the second is called centrifugal growth. Centripetal growth is seen in the infective granulomata, e.g. tuberculosis, where the cells of the tubercle are derived from the surrounding tissue cells. Such a tubercle enlarges by the successive production of new cells by the surrounding tissues. In tumours, however, this mode of enlargement is very much restricted in scope. It can only be said to occur in connection with the area of origin in certain cases. That is to say, that in certain tumours the area of origin may enlarge by successive areas in continuity with it taking on a progressive growth.

Thus papillomata are apt to extend in area by successive neighbouring portions of epithelium becoming papillomatous in addition to the true growth of the original tumour. Angeliomata, again, may enlarge by the capillaries with which it is connected successively in an increasing area taking on a progressive mode of growth. Carcinomata also may enlarge by the area of origin becoming larger, successive areas of epithelium becoming carcinomatous. Apart from the tissues in direct continuity with the area of origin, this mode of increase does not occur. In an angioma, for instance, it is only those capillaries which are in direct communication with the vessels of the tumour which take part in the enlargement. Capillaries which are not connected with it, even although they may be touching it, do not contribute to the enlargement of the tumour. It has been affirmed that the lymphocytomata of the genital organs of dogs enlarge partly by the constant addition of new cells from the surrounding tissues, but this statement is open to doubt. Centripetal growth cannot occur in tumours which are distinctly encapsulated, and it is equally inapplicable to tumours which are derived from sequestered rudiments, since these are *ex hypothesi* not in continuity with their surroundings.

Apart from this strictly limited mode of enlargement, we can say that all tumours grow by proliferation of their own cells. Their growth is intrinsic and centrifugal, and may be of two kinds: (1) central or expansive; (2) peripheral or infiltrative. Both types of growth may occur together.

In central growth, which is characteristic of the histiomata, the growth may be most active in the centre of the tumour, or may be more or less uniform throughout. We have seen that in histiomata the stroma must be considered as an essential constituent of the tumour but as subordinate to the special elements. This essential character of the stroma in histiomata has been demon-

strated in grafting experiments. It has been found possible to graft fibromata in dogs, but the grafting is successful only if circulation is set up in the blood vessels of the graft. The surrounding tissues are not capable of providing new blood vessels. In a histioma the parenchyma and stroma grow concurrently, the growth of the stroma being subsidiary to the growth of the parenchyma. The growth is thus of the same character as the growth of normal tissues. In this mode of growth the outer layers of the tumour, which always consist of connective tissue, become expanded by the more active growth of the parenchyma within them. Hence the surrounding tissues are displaced and compressed by the expansive growth of the tumour in the same way as they are compressed by the expansion of a hydatid cyst. In central growth, then, there is no mingling at the periphery of the tumour elements with the surrounding tissues. The latter are merely displaced and compressed.

In peripheral growth, on the other hand, enlargement takes place by proliferation of cells, derived from the tumour, which penetrate into the interstices of the surrounding tissues so that, at the boundary of the tumour, the tumour cells and the surrounding tissues will be found intermingled. The surrounding tissues are not so much displaced as infiltrated and destroyed *in situ*. In fact, a tumour which shows infiltrative growth *re*-places rather than *dis*-places the structures in which it is situated.

A tumour which grows by peripheral growth may, and usually does, at the same time grow centrally. The character of a tumour depends on the relative importance of the two modes of growth. A chronic scirrhus of the breast may be said to grow entirely at its periphery. In fact, in some cases, the centre may retrogress while the periphery is extending. Such a tumour shows no distinct mass increasing the size of the organ in which it is situated,

and may even show a shrinkage. On the other hand, some carcinomata and sarcomata may show central growth to such an extent as to form a large mass displacing and condensing the surrounding tissues with the formation of an apparent capsule. In such cytomata peripheral growth will be found to be present on microscopical examination passing beyond the limits of the apparent capsule.

In a cytoma growth does not necessarily take place in all parts to the same extent. One part may be growing while another part is stationary. Hence a section through one part of the margin of a cytoma may show the characteristic infiltration while a section from another part may not show it. The width of the zone of infiltration is variable, being extremely narrow in some tumours and wide in others.

Certain tumours show some peculiarities of growth. Chondromata may grow by proliferation of the chondrocytes themselves, but more frequently they grow by proliferation of the chondroblasts in the investing perichondrium. Considering the tumour as a whole, i.e. taking into account the fibrous tissue which forms the capsule and the stroma, this is a form of central growth. The case is similar in the osteomata which grow by proliferation of the osteoblasts in the periosteum or marrow, or by ossification in cartilage. Lipomata grow by the proliferation of fat-free cells in certain foci. The resulting cells from this proliferation subsequently become fat cells by the accumulation of fat within them.

The mode of growth in gliomata of the brain is not clear. These tumours rarely show a definite outline, and never project above the surface of the brain. Hence central growth apparently takes little part in the enlargement of the tumour. They either show an infiltrative growth or, as seems likely in some cases at least, they enlarge by apposition from the surrounding neuroglia.

Occasionally central growth is more marked and the tumour is encapsulated. Gliomata (gliosarcomata) of the retina enlarge by infiltrative and expansive growth.

We know little about the growth of teratomata. The enlargement of these tumours is largely due to accumulation within the cysts of the tumour, although there may be a considerable amount of growth in the more solid forms. Ovarian teratomata do not appear to have been found in foetuses and new-born children. They must therefore, it would seem, develop in post-natal life. When examined, teratomata are found to contain fully-formed tissues and organs; they do not show any evidences of active development, and there is no evidence that development proceeds in a manner at all resembling the development of the embryo. In fact, from the irregular arrangement of the different parts it would seem that it takes place in a different manner. The growth of these tumours must, in some way or other, be accompanied by development.

In blastocytomata the undifferentiated cells proliferate, and some of them become differentiated with the formation of epithelial tubes and various forms of connective tissue. These differentiated tissues continue to grow after they are formed. For example, the epithelial tubes may continue to grow, thus forming tubes which are sharply marked off with the surrounding cells. Hence it is only in some parts that the transition between the undifferentiated cells and the differentiated can be detected.

We see, then, that the histiomata and teratomata are characterised by central expansive growth displacing the surrounding parts, and the cytomata by peripheral infiltrative growth, the cells infiltrating and replacing the surrounding structures. In this infiltrative mode of growth the tumour cells wander in the tissue spaces continually proliferating. In some cases they may



FIG. 74.

Infiltrating tumour. A section through a carcinoma of the breast, showing the way in which it infiltrates the surrounding tissues. The tumour does not produce any displacement of the surrounding fat or of the overlying skin. On the contrary, the skin shows a deep depression due to the contraction of a fibrous tissue septum which passes from the tumour to the skin. See also figs. 67, 75, 76, 77, 78.

penetrate into, and proliferate in, the interior of muscle fibres or fat cells. In consequence of the pressure produced by this proliferation, any special tissues in the organ affected undergo atrophy, while the vascular supporting tissue is partly destroyed and partly remains, sometimes increased in amount, to form the stroma of the tumour. It is in this manner that the stroma of a

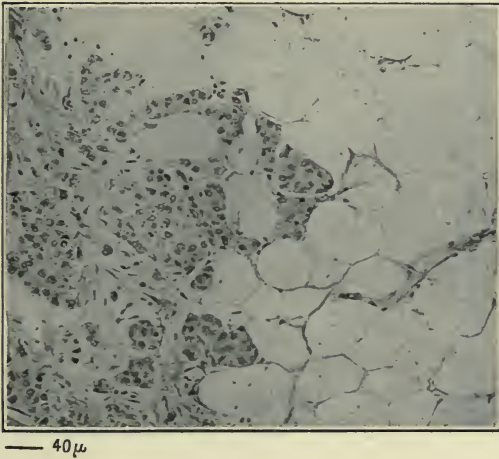


FIG. 75.

Carcinoma infiltrating fat. This is from the advancing edge of a spheroidal-celled carcinoma of the breast. Some of the cancer cells are within the fat cells. There is a marked absence of inflammatory reaction in the neighbourhood of the advancing tumour.

carcinoma is produced. It is the old stroma of the organ in which the carcinoma grows, but it may be increased or diminished in bulk. The same is true of the reticular stroma of a lymphocytoma and of the vascular part of the stroma of a sarcoma.

This fact, that the stroma is not strictly a part of the carcinoma, but is the remains of the normal supporting

tissue of the organ, has been fully confirmed by the experimental grafting of carcinomata in mice. The growth of the grafts can be followed from day to day, and it is found that the stroma of the graft degenerates and disappears while the epithelial cells remain and proliferate. Later a new stroma is produced by proliferation from the tissues at the site of implantation.



FIG. 76.

Carcinoma infiltrating muscle. This is from a case of spheroidal-celled carcinoma of the breast which was invading the pectoral muscles. Muscle fibres can be seen in various degrees of atrophy and between them are groups of cancer cells, together with lymphocytes, the latter being distinguished by their small dark nuclei.

Another fact which shows that the stroma is not an integral part of a carcinoma is the fact that in carcinoma of the lungs, whether primary or metastatic, the epithelial cells may proliferate in the pulmonary alveoli replacing the normal alveolar epithelium, the interalveolar septa becoming modified to form the stroma of the tumour.

Similarly the cells of a carcinoma invading bone sometimes form an epithelial lining to the cancellous spaces. The infiltration of a cytoma progresses to a large extent independently of natural obstacles. The infiltrating cells pass from the seat of origin into neighbouring structures penetrating fasciae, muscles, and bones with little or no hindrance. Cartilage alone, by reason of its



FIG. 77.

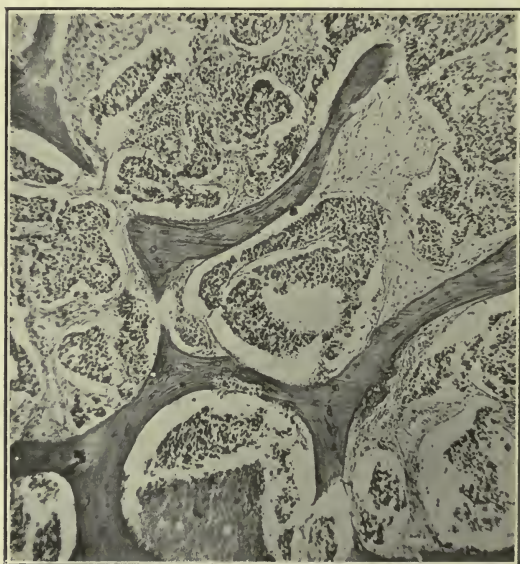
Spheroidal-celled carcinoma of the stomach, showing invasion of the muscular coat. On the left is seen the submucous coat which has been replaced by the carcinoma. Groups of carcinoma cells are seen passing between the bundles of fibres in the muscular coat.

texture and the want of sufficient spaces within it, resists the spread of a cytoma and even this is sooner or later destroyed.

Some of the cells of a tumour may wander beyond the limits of the main mass of growth and, proliferating, may give rise to distinct nodules of growth in the neighbourhood of the tumour. These separate nodules eventually become merged in the main mass of the tumour.

Dissemination.

A further step in the life history of a cytoma is met with when the cells, leaving the tissue spaces, find their way into blood capillaries or lymph channels. Here two things may happen. (1) The cells may proliferate continuously along the lymphatic or blood vessel.



— 50 μ

FIG. 78.

Carcinoma invading bone. This is from a spheroidal-celled carcinoma of the breast which had invaded a rib. Groups of carcinoma cells can be seen occupying the cancellous spaces and displacing the bone marrow.

This is known as *permeation*, and by this means of spread the tumour cells may pass for considerable distances beyond the limits of the tumour itself. Cancer cells from a carcinoma of the breast may thus reach the abdominal wall, the upper arm or the bones by con-

tinuous proliferation along the lymphatics of the deep fascia and may, here and there, give rise to distinct nodules in the skin or muscles. Similarly in some cases of abdominal carcinoma the thoracic duct may be occupied throughout its whole length by a continuous mass of carcinoma. Another example is sometimes seen in the veins in which there may be a continuous mass of

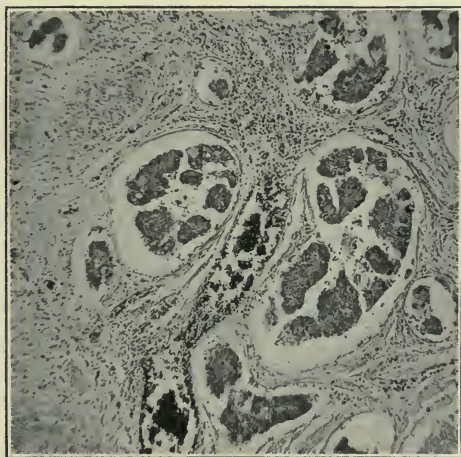


FIG. 79.

Permeation of lymphatics. Carcinoma of the breast. This is a section through a breast at some distance from the visible tumour. There are several dilated lymphatics containing groups of cancer cells. In the centre, passing up from below, is a blood vessel which does not contain any cancer cells. Above and to the left is a portion of one of the lobules of the breast.

growth filling the veins arising from the affected organ. A tumour of the testis or kidney may in this manner grow along the spermatic or renal vein into the vena cava, and so to the cavities of the heart. The direction of permeation is, to some extent, independent of the direction of flow of the blood or lymph. In a similar manner

permeation may take place along nerves or ducts to which the tumour cells have obtained access. (2) In the second place a cell which finds its way into a lymph channel or blood vessel may be carried along in the circulation until it is arrested in a distant organ such as a lymphatic gland or the lungs, liver, etc. This phenomenon is known as *metastasis*. It is characterised by the appearance of new tumours in the regional lym-

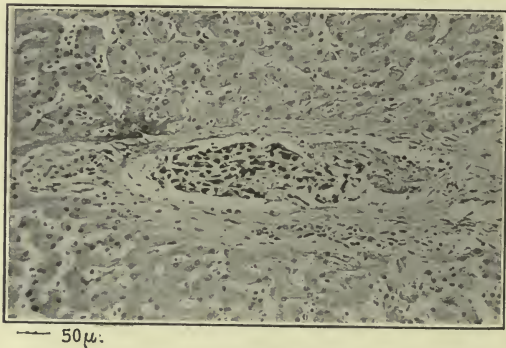


FIG. 80.

Permeation of blood vessels. Spheroidal-celled carcinoma of the stomach. A section of a branch of the portal vein in the liver, showing the cancer cells growing within it. To the right of the group of cancer cells the vein is occupied by a thrombus.

phatic glands (regional dissemination) or in distant organs (general dissemination).

The regional lymphatic glands are affected more frequently in carcinoma than in sarcoma. The glands first affected are the primary glands into which the lymphatics from the region of the tumour open. These afferent lymphatics open into the peripheral sinus of the gland and it is in this situation that the tumour cells are arrested. They then proliferate and destroy the gland. In rare instances the tumour cells may be first evident in the hilum or medulla of the gland and, in these cases, it

would appear that the cells had entered the gland by way of the efferent lymphatics by permeation against the lymph stream. The tumour cells next, by way of the efferent lymphatics, find their way to other glands (secondary glands), and so on, until the thoracic duct or right lymphatic duct is reached, when they are carried into the veins and so into the general circulation. Here they may lodge as emboli in various parts of the body and give rise to metastatic tumours. The tumour cells



FIG. 81.

Permeation of nerve sheath. Carcinoma of the stomach. This is a section of one of the nerves in the gastro-hepatic omentum. There is a zone of cancer cells separating the nerve from its sheath.

may, however, gain access to the blood stream directly from the primary tumour or at any stage from the lymphatic glands.

The distribution of metastatic tumours varies and is difficult to explain. It is easy to understand how a tumour in the viscera connected with the portal vein gives rise to metastatic tumours in the liver, and how a tumour elsewhere gives rise to metastases in the lungs, but it is difficult to understand how a carcinoma of the breast forms metastases in the liver, the lungs being

unaffected, or why in some cases metastases should occur in the ovaries or adrenals and in no other organ. In some of these cases the tumour cells may be so small that they pass through the pulmonary capillaries without being arrested, and in other cases there may be anomalies of the circulatory apparatus such as a patent foramen ovale

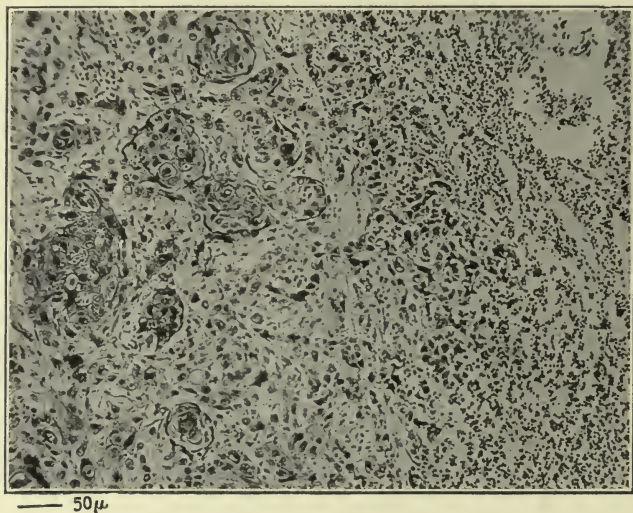


FIG. 82.

Metastatic carcinoma. Lymphatic gland. This is a section of a bronchial gland from a case of squamous-celled carcinoma of the oesophagus. On the right are seen the remains of the lymphoid tissue which, on the left, has been entirely replaced by the growth of a secondary squamous-celled carcinoma.

allowing the cells to pass into the arterial system without traversing the lungs. In rare cases there may be metastases due to retrograde embolism, i.e. to embolism in a direction contrary to the normal direction of the blood stream. Such a condition is possible in the liver owing to the temporary reversal of the blood stream in the inferior vena cava due to the respiratory movements, so that tumour cells may be forced during expiration into

the hepatic veins. Similarly the appearance of carcinoma in the left supra-clavicular glands secondary to primary carcinoma of the stomach or other abdominal organ must be attributed to cells which, after passing up the thoracic duct, have been forced back into the glands by a

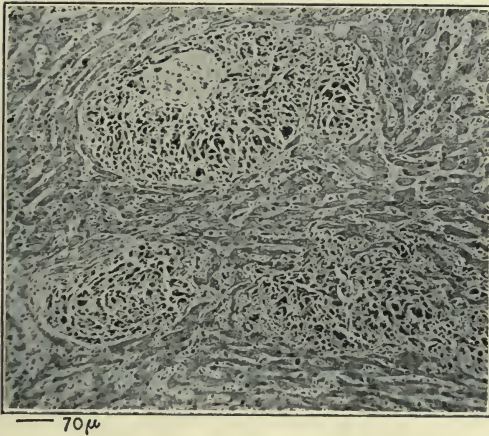


FIG. 83.

Metastatic carcinoma. Liver. A section through three small metastatic nodules in the liver secondary to a primary carcinoma of the stomach. Around the upper nodule the liver substance is becoming compressed. Above the lower right-hand nodule can be seen some cancer cells within the capillaries.

reversal of the lymph stream due to respiratory movements.

In general, however, the distribution of metastases is inexplicable. We may have a carcinoma with extensive involvement of the lymph glands and no visceral deposits, while we may find another similar carcinoma with extensive visceral tumours and no affection of the glands; or, again, we may find an extensive primary tumour without involvement of either glands or viscera.

The amount of metastasis bears no constant relation

to the size of the primary tumour. The primary growth may be very small, even microscopic, in size, and yet may give rise to extensive metastasis. For example, a minute carcinoma of the pharynx, which may be easily overlooked during life and which may be difficult of detection after death, may give rise to secondary growths in the cervical lymphatic glands which infiltrate and destroy all the structures in the side of the neck.

While the liver, lungs, and bones are frequently the seats of metastatic tumours, the spleen, muscles, and alimentary canal are rarely affected and, since we must assume that the cells in the circulation are just as likely to be carried to one organ as to another, we must suppose that these cells find the conditions in some organs more favourable for their proliferation than in others.

Primary cytomata of certain types, or of certain organs, sometimes show a peculiar distribution of metastatic growths. Metastases in the bones are most frequent in carcinomata of the thyroid, breast, prostate, and adrenals. Mammary carcinomata may give rise to metastatic tumours in the ovaries, organs which are usually not subject to carcinomata secondary to a primary in other situations. In primary carcinoma of the lung the secondary tumours are sometimes limited to the adrenals. Metastatic carcinomata of the heart are more common in the squamous-celled type than in other forms. Melanotic sarcomata show a predilection for the liver as a seat of metastasis. Rodent ulcer does not give rise to metastasis.

Metastasis in carcinoma may occasionally be so general as to take the form of a miliary carcinomatosis, the lungs and serous membranes being most affected. Such cases may, to the naked eye, closely resemble miliary tuberculosis.

The metastatic tumours more or less faithfully reproduce the characters of the primary. Not only in carcinoma are the epithelial cells similar in all respects, but the

stroma also often presents the same characters as to amount and arrangement as in the original tumour. We have seen, however, that the stroma of a carcinoma is not, strictly speaking, a part of the tumour. We must therefore conclude that the epithelial cells in a metastatic growth exert some influence on the supporting tissue of the part in which they proliferate, so that it assumes the characters of the stroma of the primary tumour. The same may be said of lymphocytomata in which the reticular stroma is derived from the surrounding tissues. This conclusion has been confirmed in the grafting experiments in mouse cancer which are comparable with the phenomena of metastasis. In these tumours, as we have seen, the stroma is not derived from the stroma of the original tumour, but is formed anew from the connective tissue at the seat of implantation. Notwithstanding this, however, the new stroma sooner or later assumes the characters of the stroma in the original tumour under the influence of the proliferating tumour cells.

Cases of carcinoma have been described in the testis and rectum in which the stroma contains cartilage. In these cases the metastatic tumours also show a cartilaginous stroma. Similarly tumours in which there is a perivascular arrangement of the cells give rise to secondary growths with the same relation of cells to stroma, and haemorrhagic carcinomata which are characterised by haemorrhages into the alveoli, give rise to metastatic tumours with the same haemorrhagic characters.

In rare cases metastasis has been found of a tumour which histologically is a histioma showing no signs of infiltrative growth. This has been found in chondromata. The majority of cartilaginous tumours which give rise to metastases are chondrosarcomata or carcinomata in which the stroma contains cartilage, but there seem to be a few cases in which the original tumour was a pure

chondroma. A chondroma by reason of its unyielding consistency may give rise to pressure ulceration of a vein which is compressed by it. The cartilage then grows into the vein and may extend for a long distance along its lumen. Thus a chondroma of the pelvis has been known to extend along the iliac veins and for some distance along the inferior vena cava. Given the presence of actively growing cartilage within a vein, it is easy to understand how a piece may be broken off and be carried to the lungs, where it may grow into a metastatic tumour. Chondromata which do not show this ulceration into and growth along the veins do not give rise to metastasis.

There are other ways in which a tumour may spread to parts of the body at a distance from the primary growth. In the first place, an ulcerated carcinoma may give rise to a carcinoma in a part of the body with which it is in contact. Thus, a carcinoma of the breast may give rise to a carcinoma of the arm or chest wall. Secondly, cancer cells may be transported along ducts and canals (e.g. alimentary canal) and give rise to tumours at a distance. Thirdly, a tumour may obtain access to one of the large serous cavities and may become disseminated throughout it. Thus an ovarian cyst may rupture into the peritoneal cavity and the epithelial cells may become distributed throughout the cavity and, becoming attached, may give rise to innumerable tumours each of which repeats the characters of the original cyst. A proliferating cyst will in this way give rise to small cysts showing the same mode of growth as the original and with similar contents. A papilliferous cyst gives rise to free papillomata or to cysts containing intracystic papillomata. Even a dermoid cyst rupturing into the peritoneal cavity may give rise to numbers of small cysts lined with squamous epithelium sometimes containing hairs. Unless the original tumour was a carcinoma, these disseminated cysts do not infiltrate the subjacent tissues, and they

often disappear spontaneously after the removal of the primary cyst.

The explanation of this disappearance appears to be that each individual secondary cyst is short-lived and disappears after a time, in this resembling the normal tissues introduced in grafting experiments. While the ruptured primary cyst is present, the secondary cysts which have disappeared are continually being replaced by new cysts derived from cells escaped from the primary. When, however, the primary cyst is removed there is no further supply of new cysts and those which are already present disappear.

Lastly, there is a method of dissemination of tumours which may be termed traumatic. If a serous cavity which is the seat of a carcinoma be tapped or explored with a syringe, the tumour may spread along the needle track and so reach the skin and subcutaneous tissue. The same may be the case in ovarian cysts. Again, in operations, cancer cells may be removed by the instruments used and grafted accidentally into the skin wound or surrounding tissues, so that tumour nodules may arise in the wound or stitch holes.

Termination.

The growth of tumours is progressive and usually continues without limit. It may show variations and may even cease for a time, but it sooner or later begins again and ceases only with the death of the patient. Some tumours, however, after growing for a time, cease, but remain permanent. Such is the case with the spongy exostoses which usually cease growing when adult age is reached and the skeleton is fully ossified. Similarly myomata of the uterus often cease growing at the menopause, and may afterwards diminish in size or become completely calcified.

There is, however, good evidence that some tumours, even cytomata, may not only cease growing, but may

retrogress and even disappear entirely. Such cases are undoubtedly rare, and in many cases of reported cure of tumours there is no doubt that inflammatory swellings have been mistaken for true tumours. No reported cure can be considered of any value unless verified by microscopical examination. Cases of the disappearance of sarcomata and carcinomata, duly authenticated, have been reported by different observers in various parts of the world. The grafted cancers in mice often show this spontaneous disappearance as do the lymphocytomata of dogs. After the tumour has grown for some time it ceases to enlarge, and then gradually diminishes in size until no trace is left. This is due to an increased activity of the stroma which, as we have seen, is produced from the tissues of the inoculated animal. The epithelial cells become broken up and removed by phagocytosis.

CHAPTER X

THE PHYSIOLOGICAL ASPECTS OF TUMOUR GROWTH

Physiological Processes in Tumours.

SEEING that the tissues and cells of which tumours are composed resemble in their anatomical characters those normally present in the organism, it may be expected that the resemblance extends to the physiological and pathological characters. Here, as elsewhere, it is impossible to distinguish sharply between physiology and pathology. Fat, for example, may be present in one tumour as an essential constituent and in another as a result of a degenerative process. We may say, in fact, that tumours are subject to the same processes as are the corresponding normal elements. The chemical composition and functional potentialities of a fibroma, chondroma, etc., are the same as those of the corresponding normal tissues. Owing, however, to the fact that the arrangement of the elements in a tumour is atypical, the function, as a rule, is not available for the use of the organism. The muscle cells of a myoma are doubtless contractile, but, owing to the lack of nerve supply and the want of suitable connections, the function is either not called into action or, if excited, is of no utility. Similarly the cells of an adenoma may secrete as do the corresponding normal cells, but, owing to the want of ducts, the secretion is of no use. Hence the secretion is liable to accumulate in the tubes and spaces of an adenoma and so give rise to retention cysts. Adenomata of the

breast may secrete a substance resembling colostrum or milk, adenomata of the liver secrete bile, sebaceous adenomata sebum, etc. The adenomata of the ovary secrete mucin or a mucinoid substance, a function which is not apparent in the normal ovary.

In some adenomata, however, the function may be available. In adenomata of the intestine, consisting as they do of tubes opening on the surface, any secretion that they produce will pass into the intestine. In tumours of the ductless glands, especially the thyroid, adrenals, and pituitary body, the secretion will also be available, but all such secretions will be in excess of the normal requirements and may be harmful.

In carcinomata the epithelial cells tend to undergo the same changes as do the corresponding normal cells. Squamous-celled carcinomata undergo keratinisation, columnar-celled carcinomata are prone to mucoid change, spheroidal-celled carcinomata of the liver secrete bile, those of the pancreas and stomach secrete the enzymes characteristic of these organs, those of the thyroid secrete colloid, and those of the adrenals are characterised by the presence of large quantities of fat and lipoids which are also found in the normal glands. These processes may occur in both primary and secondary tumours. They cannot, however, be demonstrated in all cases, and where the structure shows comparatively little resemblance to that of the tissue from which it has arisen it is unlikely that the normal functions are carried out.

In the tumours other than epithelial we find the same. The tissue of a lipoma cannot be distinguished anatomically or chemically from normal fat, yet, for some unknown reason, such fat is of no use to the body. A patient with a lipoma may, from some chronic disease, undergo extreme emaciation, but the lipoma not only may not diminish in size, but may even continue to grow steadily when all the rest of the fat in the body has disappeared. The cells of a chondroma contain fat and glycogen just as

do normal chondrocytes. Chondromata also are prone to ossification as is normal cartilage. The calcium salts in an osteoma are the same as those found in normal bone. Among the sarcomata we find that those in bones are prone to chondrify and ossify, and those starting in the choroid or in pigmented skin show the formation of melanin with the same characters as the normal pigment.

Pathological Changes.

Coming now to the changes which are more strictly pathological, we find that all the forms of degeneration and infiltration which affect other tissues also affect tumours. These changes are not always to be distinguished from the physiological processes already mentioned. Thus *fatty degeneration* is especially apt to occur in carcinomata of the breast and myomata of the uterus. Adenomata and carcinomata of the liver, myxomata, and fibromata are prone to fatty infiltration. *Colloid change* is rare apart from the tumours of the thyroid, although a substance histologically indistinguishable from colloid is occasionally found in tumours of the breast and ovary and some other tumours. The tumours commonly called "colloid cancer," but more strictly "mucoid cancer" (p. 125) are not infrequent in the stomach and intestines, where the secretion of mucus is a normal feature.

Mucoid and *hyaline change* often occur in the connective tissue of the blood vessels of a tumour and in some may occur to such an extent as to give a distinct character to the tumour. Such tumours are often called *cylindromata* from the fact that they contain more or less cylindrical structures of hyaline or mucoid material due to changes in the blood vessels or surrounding stroma. The name thus does not indicate any particular sort of tumour, which may be sarcomatous, carcinomatous, or adenomatous.

Lardaceous change may affect the blood vessels in a tumour when the patient suffers from pulmonary tubercu-

losis or other form of chronic suppuration. Corpora amylacea may be found in gliomata and in the brain tissue of teratomata.

Calcification may occur in any tumour. It may be massive, the whole tumour becoming calcified, or it may occur in the outer layers of the tumour alone or in discrete areas scattered throughout the growth. Calcification occurring in the form of small spheres or cylindrical bodies gives the character to the tumours known as psammomata. Similar bodies are sometimes found in sarcomata and carcinomata. Calcification is usually preceded by fatty degeneration or hyaline change.

Ossification may take place in any tumour and is common in tumours of bone. Ossifying sarcoma differs from osteosarcoma in the fact that in the former ossification is something added on to the tumour growth, whereas in the latter it is an integral feature of the tumour. The metastases in an ossifying sarcoma will probably not show ossification, whereas the metastases of an osteosarcoma repeat the characters of the primary. Ossification is usually preceded by calcification and sometimes by chondrification.

Haemorrhage may take place into the substance of tumours and is especially liable to occur in cytomata owing to the imperfect formation of their blood vessels, but it may also occur in lipomata, myomata, etc. In some forms of carcinoma haemorrhage is a characteristic feature of the tumour occurring in both primary and metastatic tumours.

Cysts may arise in tumours from various causes. Adenomata and carcinomata may show retention cysts due either to the accumulation of desquamated epithelial cells or to the secretion of fluid. Similarly angiomas may show retention cysts. In some tumours there may occur a mucoid change and subsequent liquefaction with the formation of a degeneration cyst. Transudation cysts may also occur as the result of oedematous infiltration.

Tumours are prone to *inflammation* and *ulceration*. This is especially liable to occur in the cytomata owing to the infiltrative mode of growth which enables them to destroy the surrounding tissues and so to become exposed on a free infected surface. Gangrene may occur as the result of inflammation or of obstruction to the blood supply.

Necrosis is very common, especially in cytomata.

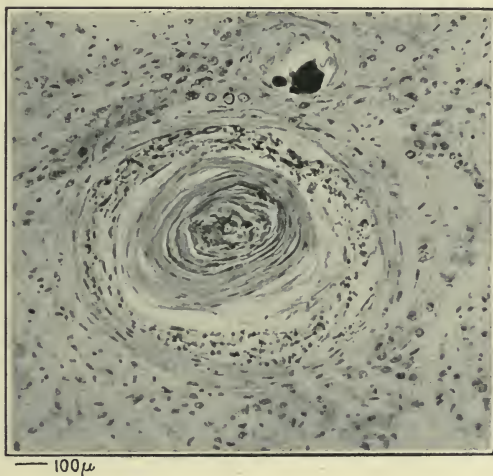


FIG. 84.

Squamous-celled carcinoma. Inflamed. Tonsil. The section shows an epithelial pearl which is invaded by numerous leucocytes.

In carcinomata the necrosis may affect the parenchyma alone or may involve both parenchyma and stroma. In the former case the cells in the neighbourhood of the stroma do not undergo necrosis, so that, where the stroma is small in amount, each blood vessel will be surrounded by a mantle of living cells thus giving the appearance of a perivascular distribution of the parenchyma.

Tumours are also liable to be the starting-point of other tumours. Thus a carcinoma may start in a papilloma,

adenoma, or teratoma, and a sarcoma may originate in a fibroma. The most interesting example of this change is seen in the case in which a sarcoma may originate in the stroma of a carcinoma. Tumours are occasionally met with which combine the characters of a sarcoma and carcinoma. In such a case the metastatic tumours may

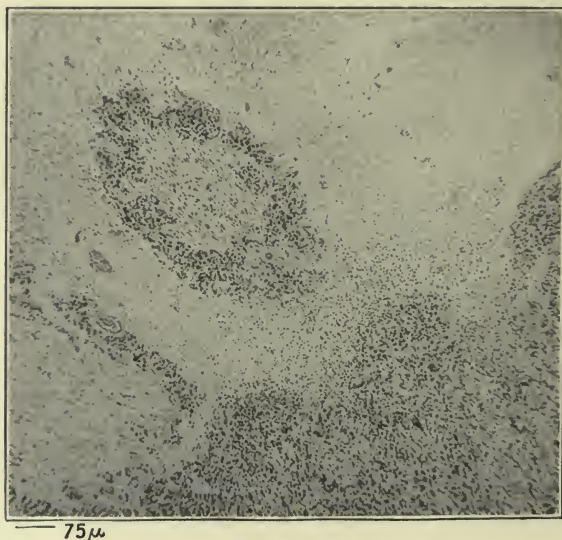


FIG. 85.

Spheroidal-celled carcinoma of the breast. Necrosis. In the upper part of this section the tumour has undergone necrosis except for a zone of healthy cells surrounding a piece of stroma which carries a blood vessel. The necrotic area appears as a mass of structureless debris in which are numerous darkly staining particles which are remains of the nuclear chromatin.

be carcinomatous, sarcomatous, or combined. Thus one may find a case of columnar-celled carcinoma of the stomach in which the stroma is sarcomatous, the secondary growths in the glands and liver being all sarcomatous. The experimental study of mouse cancer has thrown some light on these combined tumours. We

mentioned that in grafted carcinomata the stroma dies while the epithelial cells survive and proliferate, a new stroma being formed from the surrounding tissues. Occasionally, however, in the course of a series of transplantations there comes a time when the stroma does not disappear but survives and proliferates. The resulting tumour has thus the characters of a combined tumour. On further transplantation both parenchyma and stroma survive and at each subsequent experiment it is usually found that the carcinomatous element diminishes while the sarcomatous increases until the carcinomatous elements eventually disappear, leaving the tumour as a pure sarcoma which itself continues transplantable without further change.

The Effects of the Tumour on the rest of the Organism.

We have stated in our definition that tumours serve no useful purpose. This is always true if the organism is healthy apart from the particular tumour under consideration. In rare cases, however, a tumour may be temporarily useful when the patient is otherwise abnormal. If we completely remove a thyroid gland for carcinoma the patient develops the condition known as myxoedema. If at a later period a metastatic tumour develops, e.g. in a bone, the symptoms of myxoedema may disappear owing to the fact that the secretion of the tumour is able to replace the secretion of the thyroid which has been lost, and to this extent a tumour may be said to be useful. In other cases, however, any functional activity on the part of the tumour is harmful rather than useful. Adenoma or progressive hypertrophy of the pituitary body is accompanied by acromegaly which is probably due to increased pituitary secretion. Similarly adrenal tumours in children are associated with sexual precocity or adiposity.

Certain tumours have a considerable effect on metabolism. Thus multiple myelomata are associated with

the appearance of a peculiar form of protein (Bence-Jones protein) in the urine in large amounts. The origin and significance of this substance are unknown. The disease is a serious one and usually proves fatal in the course of about one year. Similarly melanotic tumours lead to the appearance of melanin in the urine.

The lymphocytomata of dogs are often associated with chronic interstitial nephritis, and it has been found possible to induce this nephritis in dogs by injecting emulsions or extracts of the tumour.

Apart from these special forms of tumours, the influence of tumours generally on metabolism is not very marked. In carcinoma there is increased alkalinity of the blood and a diminished secretion of hydrochloric acid in the gastric juice. The excretion of phosphates in the urine is diminished. The blood shows no specific changes in cancer. There is anaemia, especially in the later stages, characterised by a diminution in the number of the erythrocytes and in the colour index. There is also, in some cases, especially in sarcomata and lymphocytomata, a leucocytosis with, as a rule, no special characters: chloroma is associated with leucocythaemia, usually of the lymphoid type, but occasionally myeloid. The antitryptic power of the blood is increased. This increase also occurs in other chronic diseases. The nervous system may be affected in cancer, myelitis and neuritis being induced by the absorption of toxic substances by way of the nerve trunks.

Apart from these influences on metabolism tumours may influence the organism in other ways and are classified for clinical purposes according to the nature of the influence they exert. This influence is of two kinds: (1) the local pressure effects due to the mere presence of the growing tumour; (2) the general influence which the tumour exerts on the rest of the organism.

Tumours which only by their presence exert local pressure effects are called "simple," "benign," or

“ non-malignant ” tumours, and those which in addition exert a general disturbing influence on the organism are called “ malignant ” tumours. It must not be supposed that a simple tumour is harmless. All tumours are serious abnormalities, but a simple tumour is harmful only from its position and not from its character. A tumour of any sort within the spinal canal may cause death even if it is only of very small size, whereas a tumour such as a subcutaneous lipoma may attain a weight of several pounds without being more than an inconvenience. The local effects of simple tumours are the displacement of the surrounding parts and the resulting pressure effects, such as pressure atrophy of bone, obstruction of canals such as blood or lymph vessels, ducts, the alimentary canal or genito-urinary canal, etc. Non-malignant tumours, if they are completely removed do not recur, and the cure is complete.

Malignant tumours show the same local pressure effects, and in addition they infiltrate rather than displace the surrounding structures ; by contraction of the fibrous tissue forming their stroma the lumen of any canal in the wall of which they originate becomes constricted. They frequently give rise to metastatic tumours at a distance from the primary growth, they are apt to recur after removal, and they produce a general disturbance of the health known as “ cachexia,” which is characterised by anaemia and emaciation.

Simple tumours, then, correspond to the histiomata and teratomata and malignant tumours to the cytomata, and we have seen that the difference between these two classes of tumours is to be found in their mode of growth. Histiomata grow entirely by expansive growth, cytomata partly by infiltrative. Infiltration, then, may be taken as the histological criterion of malignancy. The tumour by this infiltrative growth spreads from the organ in which it originated into the surrounding structures, thus causing the affected organ to become fixed to its

surroundings. Recurrence after removal is explained by the widespread infiltration and permeation rendering it difficult to extirpate the whole tumour, so that groups of cells, invisible to the unaided eye, are left behind to form the nucleus of a new tumour. Sometimes recurrence takes place, not in the original site but at a distance or after a long interval of time. Some of such cases may be explained by tumour cells, either at the original site or which have been carried to a distance by the circulation, lying dormant for a time and afterwards starting to proliferate. This latency of cancer cells may be met with in experiments in mice. The appearance of a tumour may be delayed for as long as three or four months after the implantation of the graft. In other cases of late recurrence the apparently recurrent tumour may be a new tumour altogether independent of the original one.

Cachexia develops in the later stages of cancer. It is characterised by anaemia, emaciation, and digestive and nervous disturbances. It is more marked in carcinoma than in sarcoma and in ulcerated than in non-ulcerated tumours. There is no necessary connection between the amount of the disease and the severity of the cachexia. This cachexia is explained partly by the diversion of nutriment from the organism to the tumour, partly, in the case of ulcerated tumours, by the absorption of septic products and partly by the absorption of aseptic autolytic products from the necrosis and degeneration in the tumour itself. There does not appear to be any specific cancer toxin.

CHAPTER XI

THE BIOLOGICAL ASPECTS OF TUMOUR FORMATION: THE RELATION OF THE TUMOUR TO THE ORGANISM

WHAT, then, is the nature of a tumour? What is its relationship to the rest of the organism?

To guide us in answering these questions we have the following facts which we have learnt in the preceding chapters.

1. The elements of which a tumour is composed resemble anatomically, physiologically, and chemically the corresponding elements in the organism.

2. Except in the case of transplanted tumours, the rudiment from which the tumour grows is derived from the organism itself, either during development or at a later period.

3. The tumour grows by proliferation of its own elements.

4. The organomata show little power of growth, but they are characterised by development at a period when the development of the organism is complete.

5. The histiomata grow in the same way as normal tissues; the parenchyma and stroma grow *pari passu* and the stroma is to be considered as an essential but subordinate constituent of the tumour.

6. The cytomata grow by proliferation of their cells without, in the first place, any tissue formation, any tissues present being formed secondarily from the proliferating cells.

7. The functional activity of the tumour cells is of no use, but is rather harmful, to the body.

8. The growth of the tumour is entirely independent of growth in the organism and is not limited by the requirements of the body.

The relation of the tumour to the organism is thus that of a parasite to its host. In fact a tumour might be described shortly as an *autochthonous parasite*.

We have seen in the first chapter that normal development and growth must be considered as properties of the organism as a whole ; the development and growth of each part is subordinated to the requirements of the whole body. This co-ordination is brought about by intercellular influences so that the differentiation and proliferation of a particular cell depend on influences exerted upon it by neighbouring cells. If these intercellular influences are removed from any cell or complex, proliferation sets in until they are restored again. If, for instance, we remove some of the epidermis the influences exerted on the neighbouring epidermal cells are removed. Proliferation sets in and continues until the gap caused by the removal of the epidermis is filled by the cells resulting from the proliferation and then ceases (regeneration). If, now, we suppose that the influences are not restored, proliferation will continue irrespective of the needs of the organism and the cells or cell complexes will continue to grow without limit. We thus have the production of a tumour.

In a histioma, as we have seen, the parenchyma and stroma grow *pari passu*. In other words, the growth of the parenchyma and stroma in a histioma are co-ordinated *inter se*, but they are not co-ordinated with the growth of the surrounding structures. A histioma can thus be considered as a multicellular individual dependent on its surroundings for its nutriment only. It thus resembles a metazoal parasite.

In a cytoma the case is different. Here, as we have seen,

the stroma is not an integral part of the tumour, and the characteristic feature of these tumours is their growth by individual cells penetrating the surrounding tissues and proliferating there, sometimes giving rise to tissues of secondary formation. In other words, the cells of a cytoma have become freed from the control of the organism and henceforth behave as independent units and not as component parts of a higher organism. In fact a cytoma is not an individual but is a colony of individual cells and each cell may be compared to a protozoal parasite.

Cancer cells bear certain resemblances to unicellular organisms. In the first place they show a remarkable power of proliferation. Jensen's mouse carcinoma, for instance, has been propagated for over twelve years and shows no signs of diminution in vigour. At each grafting the new tumour is the direct result of the proliferation of the cells of the graft in the same way that all the bacteria in a given culture are descended from those originally introduced. The cells derived from the original tumour have thus been proliferating continuously for the whole period, which is several times the normal duration of life for a mouse. As a result of this, tumours derived from the original tumour described by Jensen are to be found in almost every pathological laboratory throughout the world.

In the next place, just as unicellular organisms such as bacteria and protozoa are apt to form associations among themselves with the appearance of characteristic colonies, so cancer cells form secondary associations with the appearance of tissues. Thus, in a carcinoma we find the secondary formation of epithelial tubes and, in a sarcoma, of cartilage, bone, etc., and the more readily such tissues are formed the less malignant is the tumour. Among carcinomata the most malignant forms are the spheroidal-celled tumours, especially those of the breast, in which the cells show little tendency to group them-

selves into tubes, while among the least malignant are the columnar-celled carcinomata in which the tendency to the formation of tubes is most marked.

Another resemblance to the lower organisms is found in the great resistance which cancer cells exhibit towards cold. While they quickly die outside the body if kept at body temperature, they can survive for weeks or months at low temperatures and can even be subjected for a short time to the temperature of liquid air without losing the power of giving rise to a new tumour when introduced into another animal.

If the cancer cell is comparable with an unicellular organism we may expect that a mouse in which a tumour has disappeared spontaneously will show the phenomena of immunity comparable with that produced in bacterial infections. We should not, however, expect that the immunity would be of the same kind as in bacterial infection because the cancer cell, being derived from mouse cells, is of the same parentage as the host, while bacteria are foreign organisms. As a matter of fact, we find that a mouse which has recovered from cancer shows an increased resistance—sometimes absolute—to a further inoculation with cancer. This increased resistance is most marked with respect to inoculation with a cancer of the same strain as the previous tumour. It is less marked in respect to other kindred strains, and there may be little or no increased resistance to a cancer of another type.

This increased resistance results from the failure of the host to produce a vascular stroma for the graft of the second inoculation. In consequence of this the greater part of the parenchyma of the graft undergoes necrosis. Only those cells which, being at the periphery, are in contact with the tissues of the host survive, and there thus results a cyst lined with epithelium and containing necrotic debris, and this cyst becomes encapsulated and eventually absorbed. The mechanism of this increased

resistance is thus different from the mechanism of acquired immunity to bacteria or to cells of an animal of a different species. Immunity in the latter case is brought about by the production, in the host, of antibodies—bacteriolysins, cytolsins, etc. Such antibodies are not formed when mouse cancer is introduced into a mouse, but they are produced when mouse cancer is inoculated into a rat. These phenomena of increased resistance to cancer are also produced in a mouse by a previous inoculation with mouse blood or mouse tissues. Neither by inoculation with mouse cancer nor by mouse tissues is any inhibitory effect produced on the growth of a tumour which is already established. The fact that inoculation of mouse cancer into a mouse does not give rise to antibodies affords strong confirmatory evidence that the cancer cells are derived from mouse cells. Similar phenomena of increased resistance are found in dogs which have recovered from the inoculable lymphocytomata.

We may therefore consider cancer as a disease due to infection by cancer cells in the same way as we consider tuberculosis as a disease due to infection by tubercle bacilli. The cancer cells, however, are directly descended from the body cells of the affected animal (or of another animal of the same species); while the tubercle bacilli are foreign organisms altogether.

CHAPTER XII

THE CAUSATION OF TUMOURS

WE have seen that the elements of which tumours are composed resemble, and are derived from, the corresponding elements of the organism, but that the growth of tumours is independent of the growth of the body and the relation of the tumour to the organism is comparable with the relation of a parasite to its host. The essential characteristic of tumours is thus not found in their anatomical structure, but in the physiological relationship of the tumour to the organism. We have now to consider the causation of this altered relationship.

The difference in size between different animals depends on the number, rather than on the size, of the constituent cells. The size of the cells in a mouse is not greatly different from that of the corresponding cells in a man. There appears to be a limit of size beyond which a cell cannot exist as such. When it approaches this limit division takes place, so that we have two cells instead of one larger cell. Normal growth is thus accompanied by cell proliferation.

If we consider a particular part of the body, for example, a single cell, we can say that its condition as regards growth at any moment is the result of the interaction of two opposing forces—the growth energy of the cell and the antagonistic influences exerted by the neighbouring cells. If these are in equilibrium no growth occurs. If, however, either the growth energy be increased or the antagonistic influences be diminished, then cell proliferation sets in.

If we consider the different factors leading to cell proliferation we find that they are the following :

1. Increased functional activity, as we have seen, leads to growth. Thus glands, muscles, etc., hypertrophy when their functional activity is increased, and tendons, fasciae, bones, etc., also hypertrophy when submitted to increased strains.

2. In some cases cell proliferation appears to be regulated by means of chemical substances (hormones) circulating in the blood. This is apparently the case in the hypertrophy of the breast and uterus in pregnancy, and probably the same is true of the proliferation of the cells of the blood-forming organs after a severe haemorrhage and of the increased production of leucocytes in suppuration, etc.

3. Removal or diminution of the antagonistic influences will set free proliferation as is seen in regeneration and in inflammation, in which the damage done by the irritant excites proliferation in the neighbouring cells.

In these three cases the proliferation is of an adaptive character and is a purely physiological process.

4. When cell proliferation has been continued for some time the cells may acquire an increased capacity for continued proliferation which may enable them to overcome more readily the antagonistic influences. This increase in proliferative capacity is seen in bacteria, both in artificial cultivation and in the body. It is also seen in metastatic tumours. Normal tissue cells injected into the circulation may show a slight amount of proliferation when they lodge as emboli in any part. Their growth energy is, however, not sufficient to overcome the restraining influences and, sooner or later, proliferation ceases and the cells are absorbed. Cells derived from a carcinoma or sarcoma, however, may, during the growth of the primary tumour, have acquired an increased amount of growth energy which enables them, when they form emboli, to continue proliferating in spite of the

restricting influences and so to give rise to metastatic tumours. That the restraining influences are greater in the case of metastatic tumours than in the case of the primary is shown by the greater tendency to encapsulation in the former. A primary tumour which infiltrates widely may give rise to metastatic tumours which are sharply limited and, in some cases, especially in the brain, may be completely encapsulated.

The increased growth energy acquired by continued proliferation is also shown in the transplantation of mouse cancers. At the first transference of a spontaneous tumour success may be obtained only in 1 % or less of the mice inoculated, whereas at subsequent transplantations the percentage of successful inoculations may successively increase until 90 or 100 % are successful.

None of these methods by which cell proliferation may be induced or increased will explain the first origination of a tumour. Many observers have thus supposed that the increased proliferative capacity may be due to an extrinsic irritant which directly stimulates the cells to proliferate. This question of a formative irritant has been hotly debated for many years. It is generally, but not universally, held at present that there is no direct stimulus to proliferation except the normal physiological stimuli mentioned above. We can consider this question, as it affects tumour causation, as follows.

No satisfactory evidence has yet been brought forward that an irritant of any kind can stimulate cell proliferation directly. All examples which apparently favour this view can be explained by the intervention of the above-mentioned physiological stimuli, the cell proliferation being an indirect result. Here, as in many other pathological conditions, it is possible to offer an explanation of the facts by means of two opposed hypotheses. The action of all known irritants on the tissues is a destructive one, any proliferation which occurs being of a secondary and adaptive nature tending to repair the damage done

by the irritant. This proliferation in the case of inflammation takes place in the surrounding tissues towards the focus of irritation, and the danger lies in the damage done by the irritant more than in the cell proliferation. In tumours—especially cancers—the condition is the opposite. Here the danger lies in the cell proliferation which takes place in the original focus, the proliferating cells spreading into the surrounding healthy tissues. In other words, in inflammation the proliferation follows on the damage done by the irritant and tends towards repair, while in cancer the proliferation is itself the cause of the damage to the surrounding tissues.

If the continued cell proliferation in tumours be the result of direct stimulation by an extrinsic irritant, such irritant must of necessity be a living organism, since the proliferation, being continuous and progressive, demands a continually increasing irritant. This applies equally to the histiomata and cytomata, and since, as we have seen, there is no sharp boundary between the two classes of tumours, we must infer that the essential causal factor is of the same nature in both cases. The supposed parasite must be either intra- or extra-cellular. If it is extra-cellular it is impossible to explain the absence of infection of the surrounding tissues, for, as we have seen, the growth of a tumour is the result of proliferation of its own cells and the surrounding tissues take no part in it except, in certain cases, in connection with the area of origin. It is affirmed by some observers that the surrounding tissues take part in the growth of the lymphocytomata of dogs, but the evidence is not altogether satisfactory. If, on the other hand, the parasite is supposed to be intra-cellular it would seem necessary to suppose that the division of the cell and of the parasite was so timed as to be simultaneous, each daughter cell receiving a daughter parasite. In all cases in which parasites are found within cells the effect is the destruction either of the parasite or of the cell.

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Since cell proliferation in tumours is similar to cell proliferation under normal conditions, the assumption of a parasite to explain it is quite unnecessary and makes an explanation of tumour growth more difficult.

Direct stimulation of cell growth by a parasite is an unknown occurrence in biology and is opposed to the facts of parasitism, and the difficulty is not avoided by applying, as some do, the term *symbiosis* as explaining the association between the supposed cancer parasite and the organism. In symbiosis the partners receive mutual benefit from the association, but symbiosis does not lead to proliferation.

Numerous micro-organisms have been described by different observers as occurring in cancers, and for many years there has been a great controversy between those who uphold and those who deny that cancer owes its origin to one or more specific parasites. Investigation has been carried out both by histological and by cultural methods and, at different times, bacilli, cocci, torulae, protozoa, myxomycetes, spirochaetes, nematode worms, and acari have been suspected as specific organisms of cancer, but no organism yet described has stood the test of criticism. No one has yet isolated from cancers any organism which will give rise to cancer when inoculated into other animals except the cancer cell itself, which, as we have seen, will, under suitable conditions, continue to live and produce cancer when grafted into an animal of the same species as that from which the cancer was derived. Recent observations appear to show that it is possible to some extent for cells, both of normal tissues and of cancers, to proliferate *in vitro* as do bacteria. Undoubtedly bacteria and other organisms may be obtained from cancers, but their occurrence is apparently accidental, or at most incidental, and they do not stand in direct causal relationship with the cell proliferation.

One other suggested stimulus to cell proliferation remains to be considered, and that is excessive nutrition.

It has been suggested that proliferation may be the outcome of excessive blood supply. Cell growth and multiplication being the result of increased assimilation, they naturally cannot occur without an adequate supply of nutriment. Increased nutriment may lead to an accumulation of storage material, e.g. fat, but it does not lead to increased proliferation, since assimilation is an active process dependent on conditions within the cell.

We come, then, to the conclusion that the only direct stimulus to proliferation is the physiological stimulus of functional activity or such physiological stimuli as act in anticipation of increased functional activity, and that extrinsic agents do not directly cause cell proliferation.

Since the capacity for proliferation is inherent in the cell, increased proliferation may be indirectly induced by removing the influences which normally keep this proliferation in check. We are quite ignorant as to the nature of these influences. We have seen that they are to be regarded as intercellular—passing from cell to cell—probably acting by means of the intercellular connections. That such influences regulating proliferation exist is shown by the phenomena of regeneration, and that intercellular influences regulate functional activity is shown by the fact that if we isolate a group of ciliated epithelial cells the cilia on all the cells continue to move rhythmically and in a co-ordinated manner as long as the cells, though isolated from their attachment, are still in contact with one another, whereas, if they are separated from one another, the co-ordination of the ciliary movement ceases, the cilia on each cell henceforth showing a rhythm independent of that of the cilia on the other cells.

The mere occurrence of increased proliferation will not, however, explain the origin of tumours. We see it also in regeneration, hypertrophy, and inflammation. In these adaptive processes, however, the proliferation is limited and purposive. It proceeds for a time, possibly somewhat

in excess of the requirements, but sooner or later comes to an end, and any excess of tissue is subsequently removed. If, for example, a bone is fractured, proliferation sets in with the formation of callus and, when the bone is healed, proliferation ceases and the excess of callus is absorbed, so that the bone returns towards the normal condition. Occasionally, however, as the result of a fracture, the proliferation continues without limit, thus leading to the formation of a sarcoma or other tumour. To express this in another way we may say that in the first case the structures of the part were originally in a condition of stable physiological equilibrium, so that the disturbance caused by the blow is followed by a return towards the original position (*recovery*). In the second case the original condition of the parts is one of unstable equilibrium and, following on the disturbance, the structures tend to depart more and more from the original position (*tumour*).

But even continued proliferation is not, of itself, sufficient to explain the origin of a tumour. We have seen that in a histioma, an adenoma for example, there is not only proliferation, but the different elements of the tumour—epithelium, blood vessels, and connective tissue—grow in a manner which shows that there is co-ordination within the tumour, while there is no co-ordination between the growth of the tumour and that of the surrounding parts.

In a cytoma, a carcinoma for example, again, there is no co-ordination between the growth of the epithelial cells and the stroma, but the epithelial cells penetrate into the, as yet unaltered, fibrous tissue, the stroma being formed subsequently from this tissue. This loss of co-ordination cannot be explained by any theory which merely attempts to account for the increased proliferative capacity. No amount of epithelial proliferation will account for its penetration into the subjacent tissues which is the characteristic feature in carcinoma.

To explain this we must assume that there is a diminution in, or loss of, the influences which normally exist between the epithelium and the connective tissue and which prevent the penetration of one into the other.

We conclude, then, that the essential causal factor in carcinoma is the continued removal of the intercellular co-ordinating influences which normally exist between the epithelium and the connective tissue. In the case of the adenoma the essential causal factor is the continued removal of the influences which exist between the tissue-complex forming the rudiment of the tumour and the surrounding tissues; and similarly for other cytomata and histiomata. The essential causal factor in tumour formation is thus an intrinsic one—an unstable condition of physiological equilibrium so that any disturbance is followed by continued growth owing to the want of those influences which normally regulate the relative position and amount of the component parts of the body.

This conclusion, however, does not lead us very far, since we are unaware of the nature of these influences. When we know the means whereby the relations of the tissues to each other, both as regards position and amount, are regulated in the normal body, then we shall be more in a position to come to a definite conclusion as to the causation of tumours.

This unstable condition of equilibrium which is the essential factor in tumour causation may be inherent in the organism or may be induced indirectly by extrinsic factors. It may be purely a local condition or limited to one group of organs, e.g. nerves or bones, or there may be a general tendency to tumour formation. We have next to consider the question, what is the cause of this instability? We may first consider extrinsic factors. These may be summed up as *chronic irritation*, which may be produced in various ways.

1. *Light* appears to be a factor in the causation of the peculiar disease known as xeroderma pigmentosa which

is followed by the appearance of multiple cutaneous carcinomata.

2. *Heat* is a factor in producing carcinoma, as is seen especially in kangri cancer. This is a carcinoma of the skin of the abdomen and thighs found among the inhabitants of Kashmir. It is due to the habit of the inhabitants of carrying under the clothing for the purpose of warmth a basket (kangri) containing a charcoal stove. The heat causes, on the skin of the abdomen and upper part of the thighs, repeated burns which are frequently followed by carcinoma.

3. Other radiations such as *X-rays* and *radium radiations* may cause carcinoma. These agents, like heat, give rise to repeated inflammatory conditions (burns) which may be followed by carcinoma.

4. Irritants of a *chemical* nature formed by the decomposition of discharges, etc. These apparently account for the large proportion of cases of carcinoma of the penis in India. This form of disease is limited to the Hindoos, while the Mohammedans, who are circumcised and cleaner in their habits, are entirely free from it. Probably also some cases of glandular carcinoma may arise from an alteration in the character of the secretion which is thereby rendered irritating.

5. *Chemical substances* derived from outside in the course of various occupations may play a part in cancer causation. Workers in soot, tar, paraffin, and the like sometimes develop carcinoma of the skin, which must apparently be attributed to their occupation. In the case of chimney-sweeps the usual seat of the tumour is the scrotum. Tar and paraffin workers may develop carcinoma of the scrotum or of the arms or other parts. Arsenic may give rise to a chronic eczema which may be followed by carcinoma. Workers in certain nickel and cobalt mines are said to be liable to lymphocytoma of the mediastinum, and workers in dye works where aniline is largely used are liable to cancer of the bladder. In some

parts of India and in the Philippine Islands and other parts of the East, cancer of the mouth is very frequent owing to the habit of betel chewing. This habit consists in chewing a mixture of tobacco, lime, and areca (or bonga) nut, wrapped in a betel leaf.

6. *Physical irritants* such as the often-quoted examples of a clay pipe or jagged tooth determining the occurrence of carcinoma of the lips or tongue. The friction of the clothing on a pigmented mole sometimes determines the development of a melanotic sarcoma. In the alimentary canal carcinoma is most frequent in those parts which are most exposed to friction, such as the orifices of the stomach, ileocaecal valve, sigmoid, and rectum. A wound or a blow may, in some cases, determine the onset of tumour formation, and a sarcoma or chondroma may develop as the result of a fractured bone. A lipoma may follow on continually repeated pressure such as carrying heavy loads on the shoulders.

7. *Chronic inflammatory conditions and scars*. Most of the above irritants give rise to inflammation which is followed in some cases by tumour formation. Other examples of chronic inflammatory conditions leading to tumour formation are leucoplakia of the tongue or vulva, chronic mastitis, cirrhosis of the liver, chronic ulcers of the leg, gastric ulcers, and Paget's disease of the nipple. Carcinoma or sarcoma may also develop in scars, the result of previous inflammatory conditions such as burns. Keloid also develops in scars.

8. *Parasites*. Specific inflammations such as lupus or syphilis may be followed by tumour growth. Similarly the inflammatory lesions caused by the ova of *Bilharzia haematobia* in the bladder may be followed by the development of papilloma or carcinoma.

We have seen that we cannot ascribe the increased proliferative capacity of the cells to specific parasites, and it does not seem possible in any other way to explain tumour growth by the assumption of a specific causal

parasite. It is impossible to account for the histiomata on this basis, and it is equally impossible to explain the complicated tumours such as blastocytomata, teratomata, and compound sarcomata. There only remain the sarcomata and carcinomata, and even in these cases the assumption of a specific parasitic origin leads to numerous difficulties. There are three possibilities to be considered.

(a) There may be a single parasite for sarcoma and carcinoma. In this case it is impossible to explain the regularity with which metastatic tumours repeat the structure of the primary. We never find a primary carcinoma giving rise to secondary sarcomatous tumours as we should expect if both were due to the same causal parasite.

(b) There may be one parasite for sarcoma and another for carcinoma. Here again the similarity of the metastatic tumours to the primary provides an insuperable difficulty. If all forms of carcinoma were due to a single parasite we should expect that metastases in the liver, in some cases at least, would show the type of hepatic carcinoma: this does not occur.

(c) Each form of sarcoma and carcinoma may have its own specific parasite. Here we are at once met with the difficulty that the different forms of these tumours are almost innumerable, corresponding to the innumerable kinds of cells in the body. While they may be reduced to a limited number of type forms, yet there is no sharp boundary between the different groups, and there is considerable variation within the limits of each group. We should have to suppose a different set of cancer parasites for each organ, and not only this, but we should have to assume a different series of parasites for each species of animal! The fact that tumours are found in all genera of the higher animals and have the same characters throughout, and yet it is impossible to graft a tumour from an animal of one species into another animal of a different species, while it is possible to do so within the

same species, tells strongly against the theory of a parasitic origin.

Other difficulties in the way of the parasitic theory are found in the close relationship of the cytomata to the histiomata and the relationship of tumours generally to malformations and to such conditions as progressive hypertrophy.

We thus see that the assumption of a specific parasitic origin for cancer leads to insuperable difficulties in explaining the observed phenomena. These difficulties entirely disappear if we consider the cancer cell itself as a parasite and cancer as a process of infection by cancer cells.

All the preceding causal factors may act in two ways. They may induce the local condition favourable to the occurrence of tumour formation, or they may, the necessary conditions being present, act as the determining factors in the origination of the tumour, or they may act in both ways. When, for instance, we find that repeated chronic irritation such as that produced by the kangri is followed by carcinoma of the skin of the abdomen while such a position for carcinoma is almost unknown among people who do not use the kangri, we may safely conclude that the repeated irritation has so altered the local conditions that the epithelial cells are able to penetrate into, and proliferate in, the connective tissue spaces. On the other hand, when we find that a blow or a fracture of a bone is immediately followed by the development of a sarcoma, whereas a similar accident in the great majority of cases has no such result, we may conclude that the necessary conditions for tumour formation were already present, and that the blow merely determined the incidence of the tumour.

Some ascribe the action of these extrinsic factors in producing carcinoma to a chronic inflammatory process in the subepithelial tissues which invade the epithelium, and thus isolate some epithelial cells from their surround-

ings. These cells, thus freed from their normal restraining influences, are able to proliferate and so to give rise to carcinoma. This preliminary isolation of epithelial cells does not, however, appear to be necessary.

9. One other factor may be here mentioned, although it is not clear how it acts. We have seen that in some cases of mouse carcinoma a sarcoma may arise from the stroma during a series of transplantations. The origination of this sarcoma appears to be in some manner dependent on the pre-existing carcinoma, but the relation between the two is unknown.

Coming now to the intrinsic factors of tumour causation, we have to rely on the evidence afforded by statistics, and especially the evidence of the mortality returns. It is necessary to bear in mind that malignant tumours are much more frequent in elderly persons and in old animals than in young individuals.

10. *Race and geographical distribution.*—It is difficult to obtain evidence as to the frequency of cancer and other tumours in the different races of man. It seems true that, while no race, with the possible exception of the Esquimaux, is known to be free from cancer, yet the civilised races are more prone to it than the uncivilised. In North America the whites are more liable to cancer than the negroes, and these, again, are more liable than their less civilised relations in Africa. Cancer is also very scarce among the North American Indians. Certain negro races are especially prone to fibromata and keloids.

The same difficulty appears regarding cancer in animals. While apparently tumours are more frequent in domesticated than in wild animals, yet the opportunities of observing tumours in wild animals are so few that no definite conclusions can be drawn on this point.

When we confine our attentions to civilised nations we find that cancer is more common in temperate regions than in the tropics. If we restrict our attention to Europe we notice that the countries in which cancer is



most frequent are Switzerland, Denmark, France, and Holland, while it is least frequent in Servia, Hungary, and Spain. It is more common in England than in Scotland, and less common in Ireland than in either. Countries with a high cancer mortality have in general a low tuberculosis mortality, and vice versa.

11. *Topographical distribution*.—If we still further restrict our observations to the distribution of cancer in a single country, we find that there are marked differences in the incidence in different districts. For example, in England and Wales the great centres of industry, such as Monmouthshire, South Wales, Durham, and Lancashire have a low cancer mortality, while in the more rural districts such as Huntingdonshire, Cambridgeshire, and North Wales the incidence is higher. In other countries, while equally marked differences in cancer incidence occur, they are not so definitely connected with differences in industrial distribution.

Cancer has been supposed to be common in valleys, the rivers of which are liable to floods, and it has been supposed to be commoner in districts which are well wooded. In some districts, however, it is commoner on the highlands, and some cancer districts are found in desert areas such as the West Australian gold-fields.

12. *Sex*.—In nearly all countries cancer is more common among females than among males. This, as we have seen, is due to the frequency of tumours of the breast and uterus, which are not comparable with the corresponding tumours in males. Omitting these, cancer is more common in males than in females, and it is increasing at a greater rate in males. - Cong
Trape

13. *Organ affected*.—In most countries the organ most frequently affected is the stomach, both in males and females. After the stomach the commonest seats of cancer in females are the uterus and the breast. In some countries cancer of the uterus is the commoner, in others cancer of the breast. In males, omitting the stomach,

the parts most frequently affected are the mouth and alimentary canal. The organ incidence differs widely in different countries. In India, for instance, cancer of the stomach is almost unknown, while the most common seats are the penis and mouth. In Kashmir the kangri cancer is the commonest.

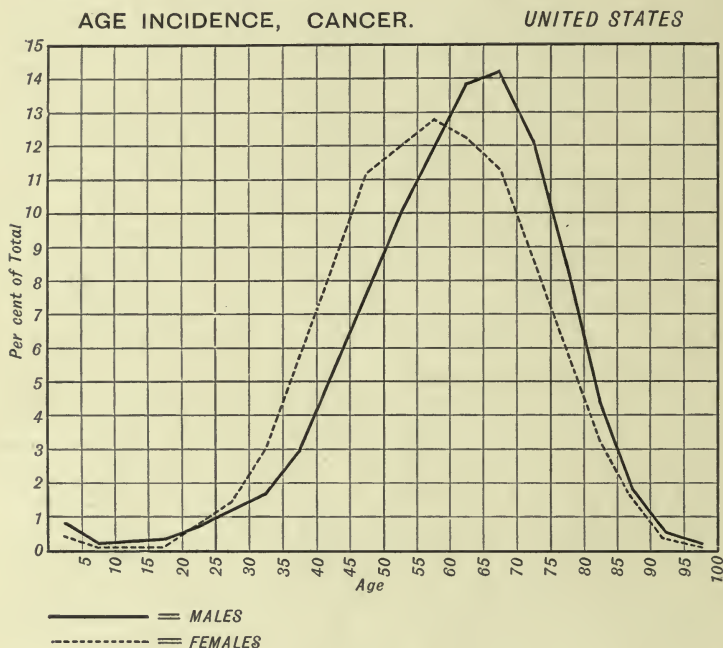


FIG. 86.

Chart showing the age distribution of carcinoma, and sarcoma combined. Carcinoma being about ten times as frequent as sarcoma, the combined curve shows the characteristics of a carcinoma curve. The maximum in females occurs ten years before the maximum in males.

14. *Age*.—If we group the cancer patients according to age we find that the maximum incidence occurs at an age, varying slightly in different countries, but usually between fifty-five and sixty-five. For instance, if we take the age at death of the carcinoma patients in America in 1900, we find that the maximum incidence in males is

in the period 65-70, and in females in the period 55-60. On each side of the maximum incidence the number of cases falls rapidly, so that when put in the form of a curve the result is a curve rising rapidly to a maximum and then falling rapidly. Such a curve is usually nearly symmetrical and uniform, showing one maximum only.

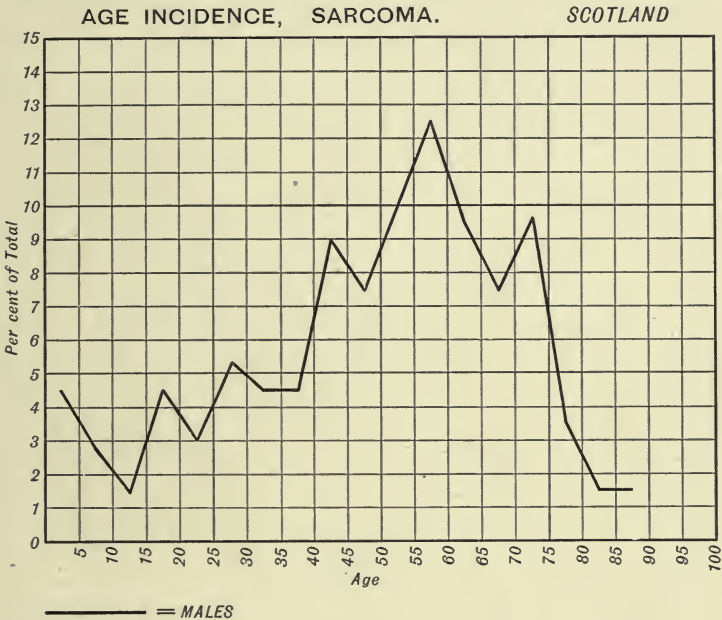


FIG. 87.

Chart showing the age distribution of sarcoma. The curve is very irregular. It starts at a comparatively high level and comes to a minimum in the period 10-15.

The rise in the curve begins about the ages 25-30. The earlier incidence in the case of females is due to the cases involving the breast and uterus which occur at an earlier age than other forms of carcinoma.

If we plot a similar curve for sarcoma we find a marked difference. Such a curve commences high owing to the congenital and early life cases, and falls to a minimum at about the age of 10. It rises during the period of

CANCER
SCOTLAND

Death Rate per 10,000 living at each age period

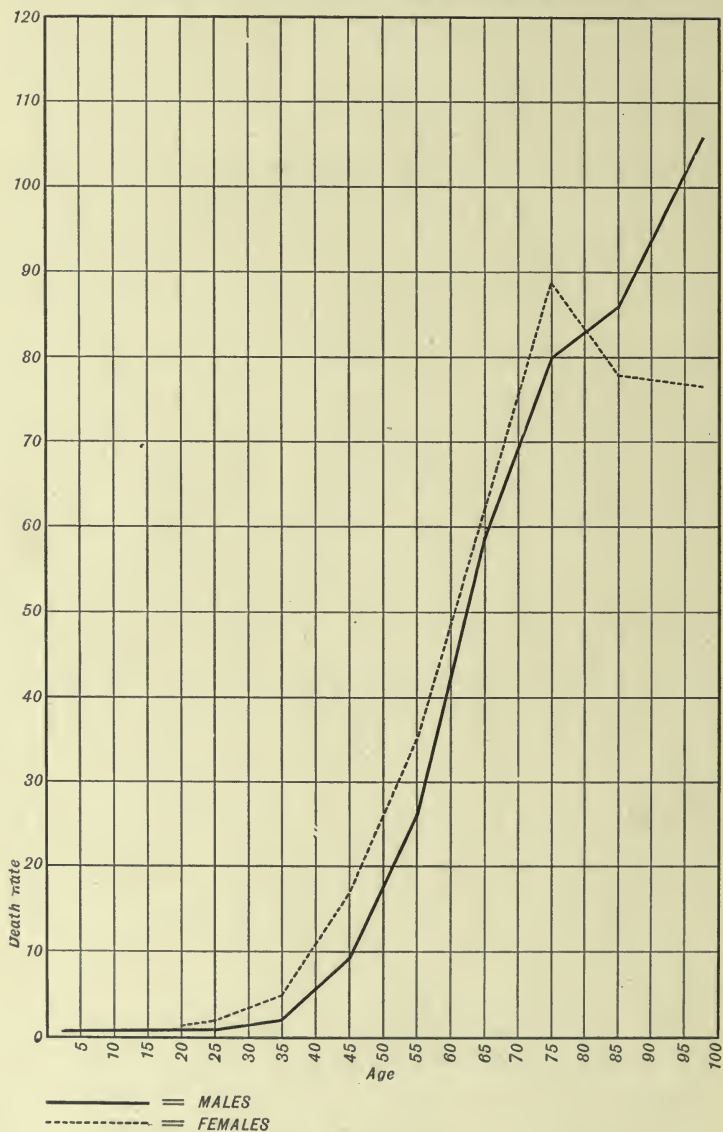


FIG. 88.

Death-rate of cancer per 10,000 living at each age period. The curve rises rapidly until it reaches the age period 70-80.

adolescence and continues at a moderately high level, showing marked variations, for the remainder of life. The two things characteristic of sarcoma curves are the minimum incidence in the period 10-15 and the rise between 15 and 25. This rise thus occurs about 10 years before the corresponding rise in carcinoma.

In both sarcoma and carcinoma if, instead of taking the absolute numbers of cases at any age, we take the number proportional to the number of persons living at each age period, we find that the curve rises continuously with increasing rapidity until about the age of 75. After this the curve most frequently falls.

The influence of age on other tumours is also marked. Blastocytomata of the kidney are almost invariably congenital or arise during the first five years of life. Similarly sacro-coccygeal and pharyngeal teratomata and blastocytomata are always congenital. Multiple exostoses and chondromata arise during youth or adolescence and the exostoses usually cease growing when growth is complete. Progressive hypertrophy of the breast usually commences immediately after puberty, and adenomata of the breast arise during adolescence. Tumours of the breast, uterus, and ovaries arise during the period of sexual activity.

15. *Heredity*.—It is extremely difficult to obtain evidence as to the influence of heredity on tumours. Undoubtedly the tendency to cancer is inherited in some cases, but instances in which the evidence is satisfactory are rare. We do occasionally meet with a family in which, for example, a large number of the females in successive generations suffer from cancer. There is no doubt that malformations tend to be inherited, and the same is true for some forms of tumour, especially molluscum fibrosum and multiple exostoses. It is found that in mice certain families are more readily inoculated with carcinoma than others, and the progeny of mice with spontaneous tumours are more than usually liable to become cancerous.

Inherited

Family
infectious
or acquired

It is difficult to draw any conclusions from the foregoing enumeration of the aetiological factors. The more carefully the distribution of cancer is investigated, the less possible it is found to associate it with any geological or physical features. Cancer increases in frequency as we depart from the equator, but otherwise it does not appear to be connected with meteorological or climatic conditions. Nor does it appear to be possible to associate the topographical distribution with different occupations. We find that in the great industrial, especially the mining, centres of England and Wales there is a low cancer mortality, while in the rural districts the incidence is higher. We cannot, however, conclude from this that the low cancer incidence in the former case is associated definitely with the occupation of mining, since we find that the distribution of cancer in females is very similar to that in males. Also in other countries the distribution of cancer does not show a similar relation to industries. It seems more probable that the difference is due to some factor which influences males and females alike, but what this factor is is not determined. Some have attributed the differences to differences in the population in respect to age, and to some extent this is no doubt true, but the highest rates of cancer mortality are not necessarily found in those parts of the country in which the inhabitants live longest. In fact, those parts of a country where the average age at death from all causes is low may show a high cancer incidence and *vice versa*. Others have associated a high cancer incidence with a high standard of living. Cancer is apparently more frequent among the well-to-do than among the very poor, and it is possible that the increase in cancer mortality which is taking place in all countries may be associated with an improvement in the standard of living.

The incidence of cancer in different occupations differs in different countries. Persons of no occupation, shopkeepers, hotel-keepers, butchers, etc., have as a rule a

high cancer mortality, and in each occupation the incidence is usually higher among the employers than among the employed.

16. *Frequency of cancer.*—The cancer death-rate in different countries of Europe varies between 1 in 10,000 in Servia and 13.5 in 10,000 in Switzerland. In England and Wales it is 9.5, and in Ireland it is 7.5 (for the year 1906). The death-rate is rising steadily in all countries for which statistics are available, and at about the same rate in each. There seems to be no doubt that this is a genuine increase, and it is not to be explained altogether by improvements in diagnosis, nor does it appear to be explained by an increased expectation of life. Carcinoma is, generally speaking, about 9 or 10 times as common as sarcoma. It is impossible to obtain reliable evidence as to the frequency of other tumours.

When all known aetiological factors have been considered, there is left over a considerable number of cases of cancer which are completely inexplicable. Such cases are analogous to the mutations and variations which play such an important part in biology. The appearance of such mutations and variations is, to some extent, dependent on alterations in the external conditions, but no direct connection can be detected between these external conditions, and the mutation, and it is often the case that mutations arise without any discoverable change in the extrinsic conditions.

To sum up our conclusion as to the causation of cancer :

1. Cancer is found in all parts of the world except, perhaps, the extreme Arctic regions, but the frequency with which it occurs differs widely in different countries and among different nations. It appears to be more common among civilised races than among uncivilised.

2. In any given country the incidence of cancer differs widely in different areas, but it has not been found

possible to associate the distribution with any geographical features.

3. The frequency with which different regions of the body are affected differs in different countries. The frequency with which a particular organ is affected depends partly on intrinsic conditions and partly on extrinsic. Thus the frequency with which the uterus, ovaries, and the female breast are affected with tumours may be readily referred to the periodical variations in functional activity to which they are subject. On the other hand, the frequency of carcinoma of the abdominal skin in Kashmir is directly attributable to the habit of carrying the kangri, and so on.

4. Chronic irritation plays a most important part in the causation of cancer. The form of irritation may vary considerably. All forms of chronic irritation lead to inflammation, and the manner in which they produce cancer may be described as follows, taking the kangri cancer as an example. The kangri produces repeated burns of the skin which may be slight or severe. This results in repeated attempts at repair, so that the epithelial cells are kept in a continued but varying condition of excessive proliferation somewhat analogous to the varying condition as regards proliferation of the cells of the breast, uterus, and ovaries. Owing to this the epithelial cells acquire an increased capacity for proliferation which enables them to overcome the restraining influences and so to proliferate to an amount in excess of the normal requirements. At the same time the repeated attacks of inflammation and ulceration lead to disturbances of the underlying connective tissue and, perhaps, to the isolation of epithelial cells from their normal connections. The epithelial cells are thus, owing to their isolation, their increased growth energy, and the alteration in the connective tissue, in a position to infiltrate the surrounding tissues and so to give rise to carcinoma. In carcinoma arising as the result of chronic

irritation increased growth energy plays an important part, and it is in accordance with this that these irritation cancers are less malignant and more amenable to surgical treatment than cancers arising independently of irritation.

5. In some cases a single blow or a wound may be followed by tumour formation. In this case we must allot the most important place to the intrinsic causal factors, the blow merely determining the incidence of the tumour.

6. Cancers and other tumours may arise spontaneously without any discoverable cause. They are in that case analogous to variations, or rather mutations, such as are met with in the propagation of plants and animals.

7. Cancers and other tumours are not attributable to specific causal parasites.

that several may be due to

8. Many tumours are more liable to occur at certain ages than at others.

9. The tendency to tumour formation appears to be inherited in some cases. Heredity, however, is by no means a general causal factor.

We thus see that we cannot attribute cancers or other tumours to any definite extrinsic factors. While some can be directly attributed to chronic irritation of various kinds, others are apparently spontaneous and are allied to mutations.

CHAPTER XIII

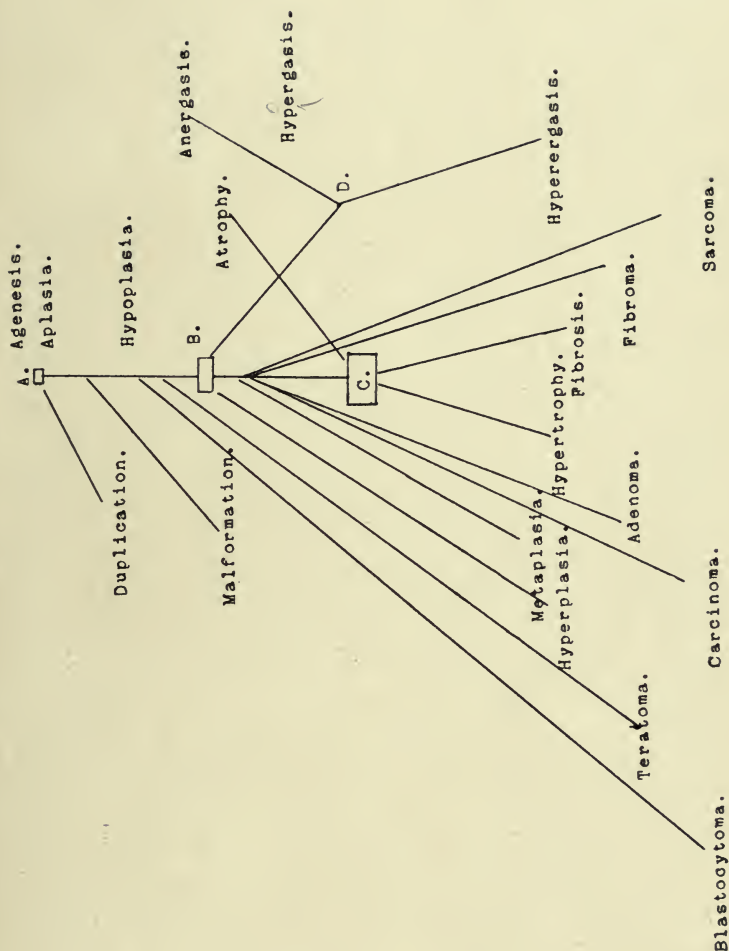
CONCLUSION

It will be useful, in conclusion, to put together some of the facts that we have learned in the preceding pages.

Let us consider the life history of any organ, a gland, for example, and study the variations to which it is subject. The organ starts as a rudiment A, and development proceeds until it reaches its normal limit B. The organ is then fully developed but small in size. It continues to enlarge during the period of growth until the growth limit is reached at C, after which it continues to remain at about the same size throughout life. At, or before, B functional activity commences and continues to increase with the growth of the organ until its limit is reached at D.

During all these stages the organ is liable to variations in the three properties of development, growth, and functional activity. If the rudiment A is not formed we have the condition *agenesis*. If the rudiment is formed but undergoes no further development, we have the condition *aplasia*. At, or before, the position A we may have duplication of the rudiment with a corresponding duplication of the resulting organ.

During any part of the period of development AB we may have the development ceasing, thus producing the condition *hypoplasia*, or the development may proceed on wrong lines giving rise to *malformations*. During this period also we may have the formation of *teratoma* and *blastocytoma*, either the tumours themselves



or the rudiments from which the tumours are subsequently formed. At B development is normally complete, but it may continue, thus producing the condition of *hyperplasia*.

During the period of growth B C we may have a change in structure—*metaplasia*. At C growth normally ceases, but, if it continues, we have the condition *hypertrophy* if the continued growth involve the parenchymatous elements, and *fibrosis* if it involve the supporting tissue. At, or after, C we may have *atrophy* setting in.

During any part of the time A C we have the formation of *tumours* or the rudiments from which tumours subsequently grow ; *adenoma* and *carcinoma* if the parenchyma is involved, *fibroma* and *sarcoma* if the supporting tissue only is affected, and *angioma* if the blood or lymph vessels are involved.

Similarly with regard to functional activity. This normally finds its limit D, and from this point we may have either retrogression—*hypoergasia* leading to *anergasia*—or increase—*hyperergasia*.

We thus have seven corresponding processes : *metaplasia*, *hyperplasia*, *hypertrophy*, *fibrosis*, *hyperergasia*, *atrophy*, *hypoergasia*. We have seen that all these processes occur in two forms—adaptive and progressive—the difference between the two being as follows. Adaptive variations are the result of definite extrinsic causal factors, are useful in nature, and come to a definite termination, the extent of the variation being limited by the needs of the organism. Progressive variations are not attributable to definite extrinsic causal factors, they are harmful in character, and are not limited by the needs of the organism. They either continue to increase without limit or they increase for a time and remain permanently in excess.

Thus the hypertrophy of a muscle following on increased work is obviously of great utility. The hypertrophy ceases when the amount of work returns to the former

level, and the muscle regains its former size. In some cases, however, a muscle hypertrophies without any increased work being thrown upon it, and continues to enlarge until it may form a large mass. Such an hypertrophied muscle is not only of no use, but is a source of great inconvenience, so that its removal is necessary.

Similarly with regard to functional activity. The increased secretion of urine in cold weather or after excessive drinking is obviously adaptive and useful. Sometimes, however, from no cause, or from only a transient cause, a permanent polyuria sets in which is not adaptive but progressive and harmful. Atrophy, again, may be adaptive when following on disuse, whereas in the progressive form it is a very serious condition.

These progressive processes thus form a well-defined group in which we must include the great group of *tumours* which may be considered as examples of progressive hypertrophy involving minute cell groups or complexes instead of the whole organ. Tumours are thus not an isolated group of disorders, but are closely allied with the rest of the progressive processes on the one hand, and, on the other, they are as we have seen linked to the malformations. The problems underlying tumour formation and tumour growth are thus akin to the problems underlying the production of malformations and the progressive processes, and the chief problem underlying the whole pathology of the progressive processes is the nature of the unstable condition of equilibrium as the result of which a process, once started, perhaps by a transient extrinsic causal factor, perhaps without any recognisable extrinsic factor, continues without any reference to the needs of the organism and without any tendency to a return to the original condition of health.

APPENDIX

GLOSSARY

Acinus (acinus, *a berry*). The secreting portion of a gland. The acini are the blind ends of the branches of the ducts, and are so called because they are grouped around the duct like berries round a branch.

Adamantinoma (ἀδάμας, *adamant*). An epithelial tumour resembling in structure the enamel organ of a developing tooth.

Adenocarcinoma (ἀδὴν, *a gland*; καρκίνωμα, *cancer*). A form of carcinoma in which there is a tendency to the formation of spaces and tubes resembling gland tubes.

Adenoma (ἀδὴν, *a gland*). A tumour characterised throughout by the presence of tubes and spaces lined with epithelium.

Adenomyoma (ἀδην, *a gland*; μῦς, *muscle*). An adenoma in which the stroma is muscular.

Adiposis (adepts, *fat*). A more or less diffuse increase of fatty tissue.

Agenesis (ἀ-, γένεσις, *production*). Absence of formation (of a rudiment).

Aletocyte (ἀλήτης, *wanderer*; κυτίς, *a small box, a cell*). A wandering cell.

Alveolus (alveolus, *a small hollow*). In a gland or a tumour an alveolus is a space bounded by the fibrous-tissue stroma and containing the epithelium.

Anaplasia (ἀνάπλασις, *a remodelling*). The reversion of cells to a less differentiated condition as a preliminary to cell division.

Anergasis (ἀν-, ἐργασία, *work*). Absence of functional activity.

Angeiectasis (ἀγγεῖον, *a vessel*; ἔκτασις, *a stretching out*). Dilatation of blood or lymph vessels.

Angeioma (ἀγγεῖον, *a vessel*). A tumour composed of blood or lymph vessels (haemangeioma, lymphangeioma). When used without any prefix it usually refers to a blood-vessel tumour.

Angeiosarcoma (ἀγγεῖον, *a vessel*; σάρκωμα, *a fleshy excrescence*). A form of cytoma in which the tumour cells show a definite perivascular arrangement. It is strictly a perivascular endothelial cytoma.

Aplasia (ἀ-; πλάσις, *a moulding*). Absence of development.

Archoplasm (ἀρχός, *a leader*; πλάσμα, *something formed*). The substance of which are formed the attraction sphere and the achromatic aster and spindle fibres of mitotic cell division. The substance which governs the process of mitosis.

Atrophy (ἀτροφία, *want of food*. ἀ-; τρέφω, *to nourish*). A diminution in size or wasting away.

Attraction sphere. The spherical mass of archoplasm surrounding the centrosome.

Autochthonous (αὐτόχθων, *of the land itself*). An autochthonous parasite is a parasite descended from the tissues of the host.

Blastocyte (βλαστός, *a sprout, germ*; κυτίς, *a small box, cell*). An undifferentiated or indifferent cell, i.e. a cell which is capable of giving rise to daughter cells of varying characters.

Blastocytoma. A tumour in which the characteristic elements are blastocytes.

Blastomere (βλαστός, *a sprout, germ*; μέρος, *a part*). A cell resulting from the segmentation of the ovum in the earliest stages before the embryo is formed.

Callus (callosus, *hard*). The mass of fibrous tissue, often containing cartilage, which is formed during the repair of a fractured bone.

Cancer (cancer, *a crab*). A term applied to any malignant tumour. The term is derived from a supposed resemblance between a malignant tumour and a crab.

Carcinoma (καρκίνωμα, *cancer*; καρκίνος, *a crab*). A term used by Hippocrates to designate a malignant ulcer. It is now restricted to the epithelial cytomata.

Carcinomatosis. A generalised outbreak of multiple (metastatic) carcinomata.

Carcinosis. A diffuse carcinomatous condition; i.e. a condition in which the cell proliferation takes place throughout a whole organ (or a large part of an organ) instead of forming a localised nodule.

Chloroma (χλωρός, *pale green*). A tumour (lymphocytoma) characterised by its green colour when freshly exposed.

Cholesteatoma (χολή, *bile*; στέαρ, *fat*). A cyst lined with squamous epithelium containing desquamated epithelial cells and cholesterin. It is usually found in the cranial cavity or in the middle ear.

Chondroblast (χόνδρος, *gristle, cartilage*; βλαστός, *a sprout*). The chondroblasts are the cells of the perichondrium which form cartilage.

Chondrocyte (χόνδρος, *cartilage*; κυτίς, *a cell*). A cartilage cell.

Chondroma (χόνδρος, *cartilage*). A tumour in which the characteristic element is cartilage.

Chondrosarcoma (χόνδρος, *cartilage*; σάρκωμα, *a fleshy mass*). A sarcoma in which there is a formation of cartilage from the tumour cells.

Chordoma (χορδή, *a string*). A tumour composed of tissue of the same nature as that of the notochord.

Chorionepithelioma (χόριον, *chorion*; epithelioma). A tumour composed of syncytia and polygonal cells derived from the chorionic epithelium of the placenta.

Colloid (κόλλα, *glue*; είδος, *likeness*). A substance of a glutinous consistency found in the thyroid gland and occasionally in other situations. The name is sometimes given to the mucoid substance found in some carcinomata, especially those of the stomach and intestines.

Condyloma (κονδύλωμα, *a knob*). A wart. The name is especially given to warts of venereal origin.

Cylindroma. A name given to certain tumours in which there is a hyaline or mucoid transformation of the blood vessels and surrounding structures resulting in the formation of more or less cylindrical hyaline bodies throughout the tumour.

Cytoma (κυτίς, *a cell*). A tumour in which the characteristic elements are cells not forming definite tissues.

Desmocyte (δεσμός, *a bond*; κυτίς, *a cell*). A general term implying any kind of supporting tissue cell.

Desmocytoma. A tumour composed of desmocytes = sarcoma.

Desmoma (δεσμός, *a bond*). A tumour composed of any kind of supporting tissue.

Elephantiasis (ἐλεφαντίασις). A condition in which there is a great thickening of the skin and subcutaneous tissue so as to make it resemble an elephant's hide.

Endothelioma. An endothelial cytoma.

Endothelium (badly derived by analogy with epithelium). A kind of epithelium consisting of a membrane of flattened cells. It is found in the blood vessels, serous membranes, pulmonary alveoli, etc.

Epithelioma. The term epithelioma is usually used as equivalent to squamous-celled carcinoma, although some authors talk of columnar-celled epithelioma. In France epithelioma is used in the sense of carcinoma generally.

Epithelium (ἐπί, *upon*; θηλή, *a nipple*). The term epithelium was originally given to the epidermis from the fact that it rests on the dermal papillae, and was afterwards extended to other surface membranes. From this word there have been formed by analogy the words *endothelium* and *perithelium*, terms which, in themselves, are meaningless in this connection.

Epulis (ἐπί, *upon*; οὖλις, *gums*). A tumour of the gums.

Erythrocythaemia (ἐρυθρός, *red*; κυτίς, *a cell*; αἷμα, *blood*). A condition in which there is an increase of red blood corpuscles in the circulating blood.

Exostosis (ἐξόστωσις: ἐξ, *out of*; ὀστέον, *bone*). A bony tumour growing in continuity with the bone in which it is situated.

Fibrocyte (fibra, *a fibre*; κυτίς, *a cell*). A fibrous tissue cell.

Fibroma (fibra, *a fibre*). A tumour composed of fibrous tissue.

Fibromatosis = multiple fibromata.

Fibrosarcoma (fibra, *a fibre*; σάρκωμα, *a fleshy excrescence*). A sarcoma in which there is development of fibrous tissue from the tumour cells.

Fibrosis (fibra, a fibre). A diffuse overgrowth of fibrous tissue.

Ganglion (γάγγλιον, a subcutaneous tumour connected with tendons). This name is applied to a swelling connected with the tendons of the hand or foot. Some of these are cystic dilatations of the tendon sheath, while others are myxomata.

Glioma (γλία, glue). A tumour composed of neuroglia.

Gliosarcoma (γλία, glue; σάρκωμα, a fleshy excrescence). A sarcoma of neuroglia cells in which neuroglia is formed in the older parts of the tumour.

Gliosis (γλία, glue). A diffuse overgrowth of neuroglia.

Hamartoma (αμάρτημα, a failure). A tumour due to a failure of development.

Histioma (ιστίον, a web or net, hence a tissue). A tumour composed entirely of formed tissues.

Hygroma (ὕγρως, fluid). A name given to the subcutaneous cystic lymphangiomas.

Hyperergasia (ὑπέρ, over; ἐργασία, work). Increased functional activity.

Hypergasia (ὑπό, under; ἐργασία, work). Diminished functional activity.

Hypernephroma (ὑπέρ, over; νεφρός, kidney). A name sometimes given to adrenal tumours, whether arising in the adrenal itself or from adrenal rests in other organs.

Hyperplasia (ὑπέρ, over; πλάσις, a moulding). This term is used in this book in the strict sense of excessive development. It is often used as implying numerical hypertrophy.

Hypertrophy (ὑπέρ, over; τρέφω, to nourish). Overgrowth (literally excessive nourishment).

Hypoplasia (ὑπό, under; πλάσις, a moulding). Underdevelopment.

Karyolysis (κάρνον, a kernel; λύσις, solution). Solution of the nuclear chromatin.

Karyorrhexis (κάρνον, a kernel; ῥήξις, a breaking). Breaking up of the nuclear chromatin into small fragments.

Keloid (κήλη, a tumour, or κηλὶς, a blemish; εἶδος, appearance). A form of fibroma which is apt to originate in a scar.

Leiomyoma (λεῖος, smooth; μῦς, muscle). A tumour composed of smooth muscle.

Lipoma (λίπος, fat). A tumour composed of fat tissue.

Lymphadenoma (lymphā, water; ἀδὴν, gland). A tumour composed of tissue resembling that of a lymphatic gland (=lymphoma). The name is often applied to a progressive enlargement of lymphatic glands such as is found in Hodgkin's disease.

Lymphocytoma (lymphā, water; κυτίς, cell). A cytoma in which the characteristic cells are cells resembling the mother-cells of the lymphocytes such as are found in the germ centres of lymphatic glands.

Lymphoma (lymphā, water). A tumour composed of lymphoid tissue.

Lymphosarcoma = lymphocytoma.

Macrocheilia (μακρός, large; χεῖλος, lip). An enlargement of the lip usually due to angeiectasis.

Macroglossia (μακρός, large; γλῶσσα, tongue). An enlargement of the tongue due, most frequently, to angeiectasis.

Medullary (medulla, marrow). A term applied to soft cancers because of their brain-like consistency.

Melanotic (μέλας, black). A term applied to tumours coloured brown or black by the presence of melanin.

Metaplasia (μετά, change; πλάσις, a moulding). Change of structure.

Metastasis (μετάσταςις, a removal to a different place). The generalisation of a tumour by the formation of secondary tumours in distant organs. The term is also applied to septic infections—e.g. in pyaemia.

Metergasis (μετά, change; ἐργασία, work). Change of function.

Molluscum fibrosum. A term applied to the soft fibromata found in v. Recklinghausen's disease.

Myeloma (μυελός, marrow). A tumour composed of bone marrow.

Myocyte (μῦς, muscle; κυτίς, cell). A muscle cell.

Myocytoma (μῦς, *muscle*; κυτίς, *cell*). A cytoma in which the characteristic cells are muscle cells.

Myoma (μῦς, *muscle*). A tumour composed of muscular tissue.

Myoplasm (μῦς, *muscle*; πλάσμα, *something formed*). The contractile portion of a muscle fibre as opposed to the sarcoplasm or undifferentiated portion.

Myxocyte (μύξα, *mucus*; κυτίς, *cell*). A mucus tissue cell.

Myxoma (μύξα, *mucus*). A tumour composed of mucus tissue.

Myxosarcoma (μύξα, *mucus*; σάρκωμα, *a fleshy mass*). A sarcoma in which there is a formation of mucus tissue.

Neurocyte (νεῦρον, *a tendon or nerve*; κυτίς, *a cell*). A nerve cell.

Neurocytoma (νεῦρον, *a nerve*; κυτίς, *a cell*). A cytoma in which the characteristic elements are nerve cells.

Neurofibroma = fibroma of nerve.

Neuroma (νεῦρον, *a nerve*). A histioma in which the characteristic features are the presence of nerve tissue.

Odontoma (ὀδούς, *a tooth*). A tumour in which the characteristic feature is the presence of dentine. The term is also applied to any tumour of the teeth.

Organoma (ὄργανον, *an organ*). A tumour characterised by the presence in it of definite organs.

Osteocyte (ὀστέον, *a bone*; κυτίς, *a cell*). A bone cell.

Osteoid sarcoma (ὀστέον, *a bone*; εἶδος, *likeness*). A sarcoma in which there is the formation of non-calcified bony tissue (osteoid tissue).

Osteoma (ὀστέον, *a bone*). A tumour composed of bone.

Osteosarcoma (ὀστέον, *a bone*; σάρκωμα, *a fleshy mass*). A sarcoma in which there is formation of bone from the tumour cells.

Papilocarcinoma (papilla, *a pimple or nipple*; καρκίνωμα, *cancer*). A carcinoma in which there is the formation of papillary excrescences.

Papilloma (papilla, *a pimple or nipple*). A tumour consisting of processes of fibrous tissue covered with epithelium,

Parenchyma (παρέγχυμα, παρα, *beside*; ἐγχέω, *to pour in*). A term originally applied to the substance of the liver and kidneys. It is now used to denote the special structures in an organ or tumour as opposed to those structures which merely act as a support and are called the stroma.

Pedunculated (pedunculus, diminutive of pes, *a foot*). Furnished with a foot or stalk. Applied to tumours which are connected with their surroundings by a narrow stalk.

Perithelioma. A name sometimes given to the perivascular endothelial cytomata. The name itself is meaningless. (See under *Epithelium*.)

Permeation (permeo, *to pass through*). The extension of cytomata by continuous growth along natural channels.

Polypus (πολύπους, nasal *polypus*; πολὺς, *many*, πούς, *foot*). Any pedunculated piece of tissue projecting into a cavity. It may be a tumour or a swollen piece of mucus membrane, etc.

Progressive processes. The progressive processes are those processes which continue irrespective of the needs of the organism.

Psammoma (ψάμμος, *sand*). A tumour containing calcareous particles like grains of sand.

Rhabdomyoma (ράβδος, *a rod or stripe*; μῦς, *muscle*). A tumour composed of striated muscle.

Sarcoma (σάρκωμα, *a fleshy excrescence*). A cytoma which is composed of desmocytes (supporting tissue cells) = desmocyto-
cytoma.

Sarcomatosis. An outbreak of multiple sarcomata, either primary, or as the result of metastasis.

Sarcoplasm (σάρξ, *flesh*; πλάσμα, *something formed*). The unspecialised protoplasm of a muscle fibre as opposed to the myoplasm or contractile substance.

Sarcosis. Diffuse sarcoma affecting the whole of an organ simultaneously and not forming definite nodules.

Scirrhus (σκῆρος, *a hard tumour*). A hard tumour. A clinical term applied especially in cases of hard carcinomata.

Sessile (sessilis, *fit for sitting upon*). A term applied to projecting tumours in which the base is at least as broad as the projecting portion of the tumour. Opposed to pedunculated.

Stroma (στρώμα, *a mattress*). The connective tissue framework of an organ or tumour which supports the essential elements and carries the blood vessels.

Syncytioma (σύν, *together*; κυτίς, *cell*). A tumour characterised by the presence of multinucleated masses of protoplasm (syncytia).

Syringomyelia (σὺριγξ, *a tube*; μυελός *marrow*). A condition of the spinal cord in which there is a diffuse gliosis with cavity formation extending for some distance along the cord.

Teratoma (τέρας, *a monster*). A tumour in which organs such as skin, teeth, etc., are present without definite arrangement.

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